

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07C 65/21, A61K 31/085, 31/19, 31/235, C07C 69/76, 205/35, 205/57, 311/02, 311/51, 235/42, 235/34, 217/58, 217/80, 219/14, 255/54, 271/02, 259/10, C07D 213/79, 239/10, 401/14, 401/06, 207/26, 311/22, 279/16, 237/14, 471/04, 235/06, 333/38, 257/04, 209/42, 277/32, 277/22, 277/64, 513/04, 498/04, 285/12, 233/60, 231/12, 235/18, 233/90, A61K 31/16, 31/325, 31/275, 31/135, 31/35, 31/38, 31/395 // (C07D 471/04, 235:00, 221:00) (C07D 513/04, 277:00, 221:00) (C07D 498/04, 263:00, 221:00)</p>	A1	<p>(11) International Publication Number: WO 94/12461</p> <p>(43) International Publication Date: 9 June 1994 (09.06.94)</p>
<p>(21) International Application Number: PCT/US93/10228</p> <p>(22) International Filing Date: 29 October 1993 (29.10.93)</p> <p>(30) Priority Data: 07/984,408 2 December 1992 (02.12.92) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 07/984,408 (CIP) Filed on 2 December 1992 (02.12.92)</p>	<p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DUPLANTIER, Allen, J. [US/US]; 450 Pumpkin Hill Road, Ledyard, CT 06339 (US). EGGLE, James, F. [US/US]; 184 Elm Street, Stonington, CT 06378 (US). MARFAT, Anthony [US/US]; 333 Lantern Hill Road, Mystic, CT 06355 (US). MASAMUNE, Hiroko [US/US]; 68 High Street, Noank, CT 06340 (US).</p> <p>(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(81) Designated States: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: CATECHOL DIETHERS AS SELECTIVE PDE_{IV} INHIBITORS</p> <p>(57) Abstract</p> <p>This invention relates to 4-substituted catechol diether compounds which are selective inhibitors of phosphodiesterase (PDE) type IV. The compounds of the present invention are useful in inhibiting PDE_{IV} and in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases. This invention also relates to pharmaceutical compositions comprising the compounds hereof.</p> <div style="text-align: right; margin-top: 20px;"> </div>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

-1-

CATECHOL DIETHERS AS SELECTIVE PDE_{IV} INHIBITORSBackground of the Invention

This invention relates to a series of 4-substituted catechol diether compounds which are selective inhibitors of phosphodiesterase (PDE) type IV and as such are useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases.

This invention also relates to the pharmaceutically acceptable salts of said compounds; to a method of using such compounds in the treatment of inflammatory conditions in mammals, especially humans; and to pharmaceutical compositions useful therefor.

The "inflammatory conditions" which can be treated according to this invention include, but are not limited to, chronic obstructive pulmonary disease, shock, atopic dermatitis, bronchitis, rheumatoid arthritis and osteoarthritis.

Since the recognition that cyclic AMP is an intracellular second messenger (E. W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases have been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo and D. H. Reifsnyder, TiPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, R. A. Challiss and M. Shahid, TiPS, 1991, 12, 19). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M. W. Verghese *et al.*, J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects.

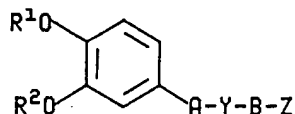
Certain pyrimidone compounds have been disclosed to be useful as antidepressants by Saccomano *et al.*, in European Patent Application EPO 247 725 A2. The same pyrimidone compounds have been disclosed to be useful against asthma and certain skin disorders in International Patent Application No. PCT/US90/02162, filed April 20, 1990.

-2-

Summary of the Invention

This invention is concerned with a series of 4-substituted catechol diether compounds and to the pharmaceutically acceptable salts of such compounds. These new compounds possess antiinflammatory activity in mammals, especially humans.

The compounds of the present invention are of the formula (I)



(I)

the racemic-diastereomeric mixtures and optical isomers of compounds of formula I and the pharmaceutically acceptable salts thereof wherein

R^1 is selected from the group consisting of methyl, ethyl, difluoromethyl and trifluoromethyl;

R^2 is selected from the group consisting of (C_1-C_6) alkyl, alkoxyalkyl having 3 to 7 carbons in the alkoxy portion and 2 to 4 carbons in the alkyl portion, phenoxyalkyl having 2 to 6 carbons in the alkyl portion, (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion, phenylaminoalkyl having 2 to 6 carbons in the alkyl portion and the amino may be optionally substituted with (C_1-C_4) alkyl and indanyl,

where the alkyl portion of said alkyl, phenoxyalkyl, cycloalkyl, polycycloalkyl, phenylalkyl and indanyl may optionally be substituted with one or more fluorine atoms, -OH or (C_1-C_4) alkoxy,

and the aryl portion of said phenylalkyl, phenoxyalkyl and indanyl may optionally be substituted with (C_1-C_4) alkyl, (C_1-C_4) alkoxy or halogen;

A and B are independently selected from the group consisting of a covalent bond, optionally substituted (C_1-C_5) alkylene, optionally substituted (C_2-C_5) alkenyl and optionally substituted phenylene,

where said optionally substituted alkylene may be monosubstituted and each substituent is selected from the group consisting of oxo, (C_1-C_4) alkoxy, CO_2R^6 and hydroxy,

said optionally substituted alkenyl may be monosubstituted with (C_1-C_4) alkoxy or CO_2R^6 , and

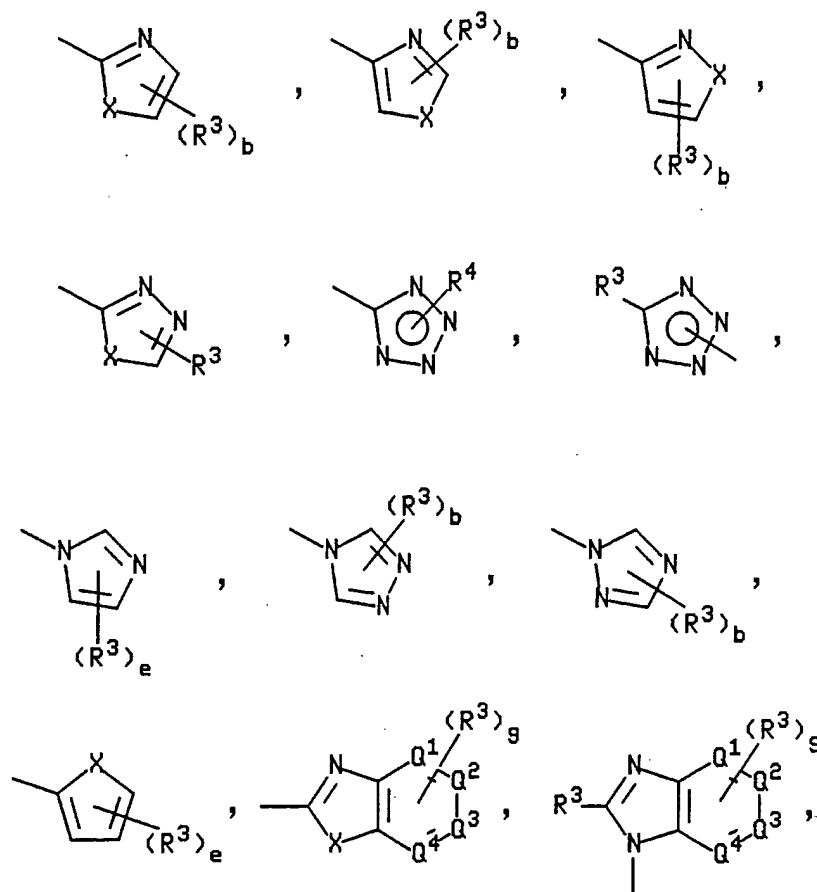
-3-

said optionally substituted phenylene may be monosubstituted with (C₁-C₄)alkoxy, CO₂R⁶ or hydroxy,

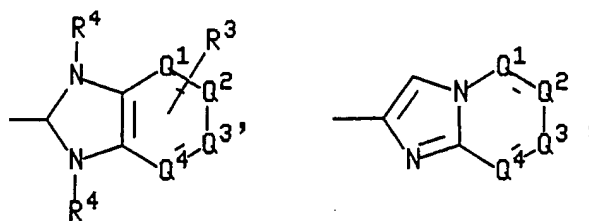
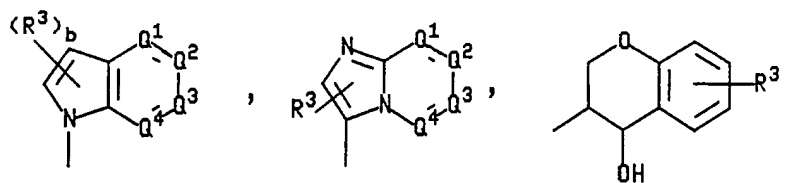
wherein R⁶ is hydrogen or (C₁-C₄)alkyl;

Y is selected from the group consisting of a covalent bond, O, NR⁶ and S wherein R⁶ is as defined above;

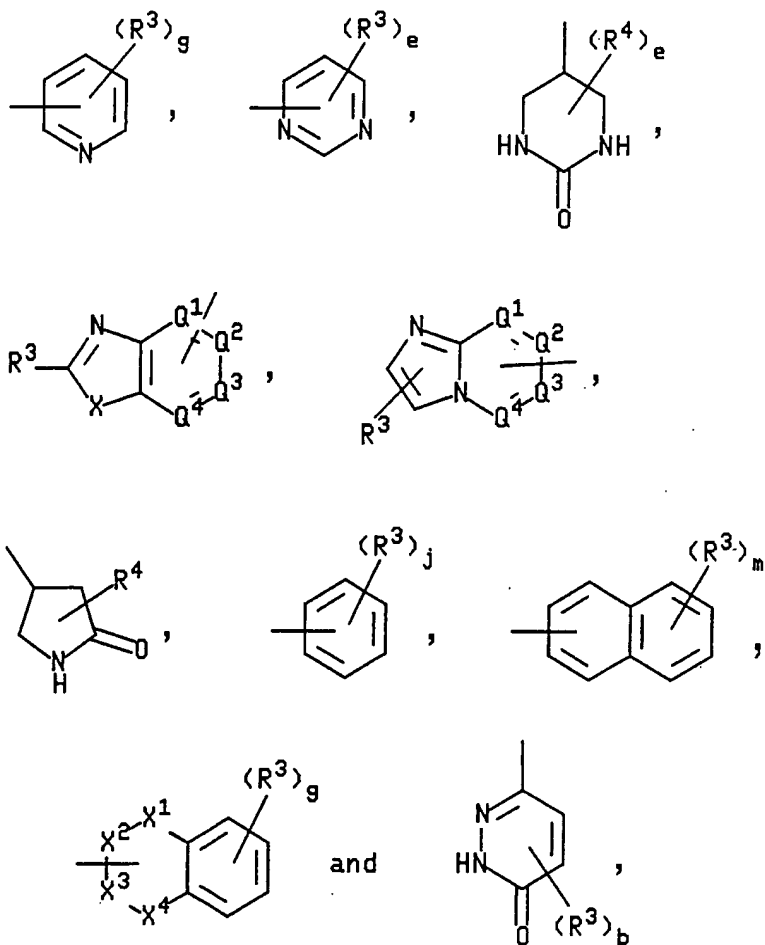
Z is selected from the group consisting of



-4-



-5-



where Q^1 , Q^2 , Q^3 , and Q^4 are independently N, CH or, when also bonded to B, C and provided that at least two of Q^1 , Q^2 , Q^3 , and Q^4 are not N;

X is selected from the group consisting of O, NR^4 and S;

and X^1 , X^2 , X^3 and X^4 are independently selected from the group consisting of O, NR^4 , S, C=O, CH_2 and, when also bonded to B, CH;

b is an integer from 1 to 2;

e is an integer from 1 to 3;

g is an integer from 1 to 4;

j is an integer from 1 to 5;

m is an integer from 1 to 7;

each R^3 is independently selected from the group consisting of hydrogen, halogen,

-6-

(C₁-C₆)alkyl, CH(R⁷)CO₂R⁴, (C₁-C₆)alkoxy, CO₂R⁴, CONR⁴R⁵, CONHOH, CH₂NR⁴R⁵, NR⁴R⁵, nitro, hydroxy, CN, SO₃H, phenylalkyl having 1 to 4 carbons in the alkyl portion, SO₂NR⁴R⁵, N(SO₂R⁶)₂ and NHSO₂R⁶,

where R⁴ for each occurrence is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, phenyl optionally substituted with (C₁-C₄)alkyl or halogen, CH(R⁷)CO₂R⁶, (C₃-C₇)cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion and dialkylaminoalkyl having a total of 5 carbons in the dialkylamino portion and having 2 to 5 carbons in the alkyl portion where R⁶ is as defined above,

R⁵ for each occurrence is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion, phenyl, pyridyl, pyrimidyl, thiazolyl and oxazolyl,

or R⁴ and R⁵ are taken together with the nitrogen to which they are attached and form an optionally substituted saturated or unsaturated 5- or 6-membered ring, a saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms, or a quinoline ring optionally substituted with fluoro,

where said optionally substituted saturated or unsaturated 5- or 6-membered ring may be mono- or di-substituted and each substituent is independently selected from the group consisting of alkyl having 1 to 4 carbons, CO₂R⁷ wherein R⁷ is as defined below, CONH₂, CON(CH₃)₂, oxo, hydroxy, NH₂ and N(CH₃)₂, and said saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms has the second heteroatom selected from the group consisting of O, S, NH, NCH₃, NCOCH₃ and NCH₂Ph;

R⁷ for each occurrence is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl;

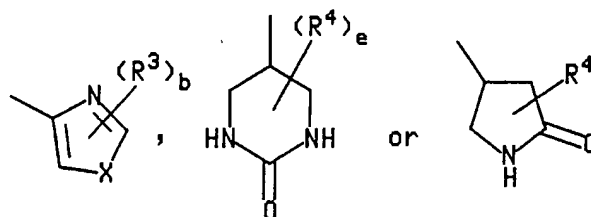
and R⁸ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, phenyl and phenylalkyl having 1 to 4 carbons in the alkyl portion;

-7-

with the proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9) polycycloalkyl or indanyl; A, B and Y are covalent bonds; X is N; and R^3 is hydrogen;

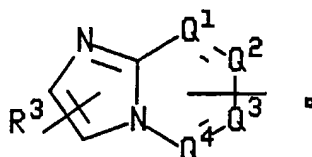
then Z is not



and with the further proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9) polycycloalkyl or indanyl; A, B and Y are covalent bonds; Q^1 , Q^2 , Q^3 , and Q^4 are CH or, when bonded to B, C; and R^3 is hydrogen;

then Z is not

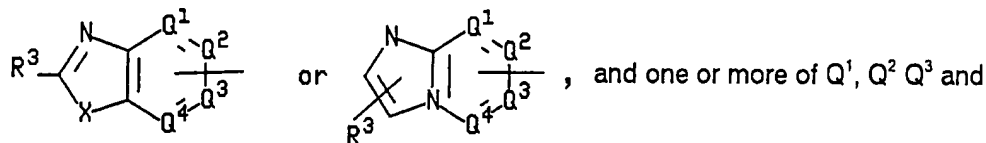


As used throughout this specification and the appendant claims, the terms "alkyl" and "alkoxy" include both straight chain and branched groups; the term "halogen" includes fluoro, chloro and bromo; and the symbol "Ph" in the term "NCH₂Ph" means phenyl.

Those members of the substituent Z which are bicyclic are attached to the remainder of the compound of formula (I) through the ring of the Z substituent in which the bond is drawn.

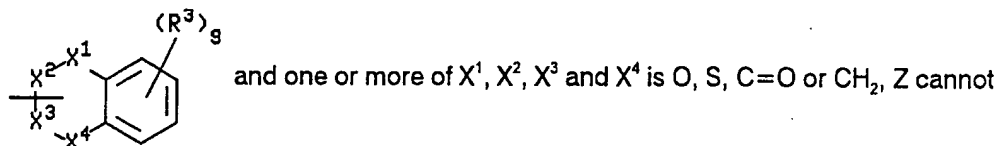
-8-

As will be readily apparent to one skilled in the art, when Z is either



Q^4 is N, Z cannot be bonded through one of its ring nitrogen atoms to the rest of the molecule.

Further, it will also be readily apparent to one skilled in the art, when Z is



be bonded through one of the above-named atoms or groups to the rest of the molecule.

A preferred group of compounds is that group of compounds of formula (I), above, wherein

R^1 is selected from the group consisting of methyl and difluoromethyl;

R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion;

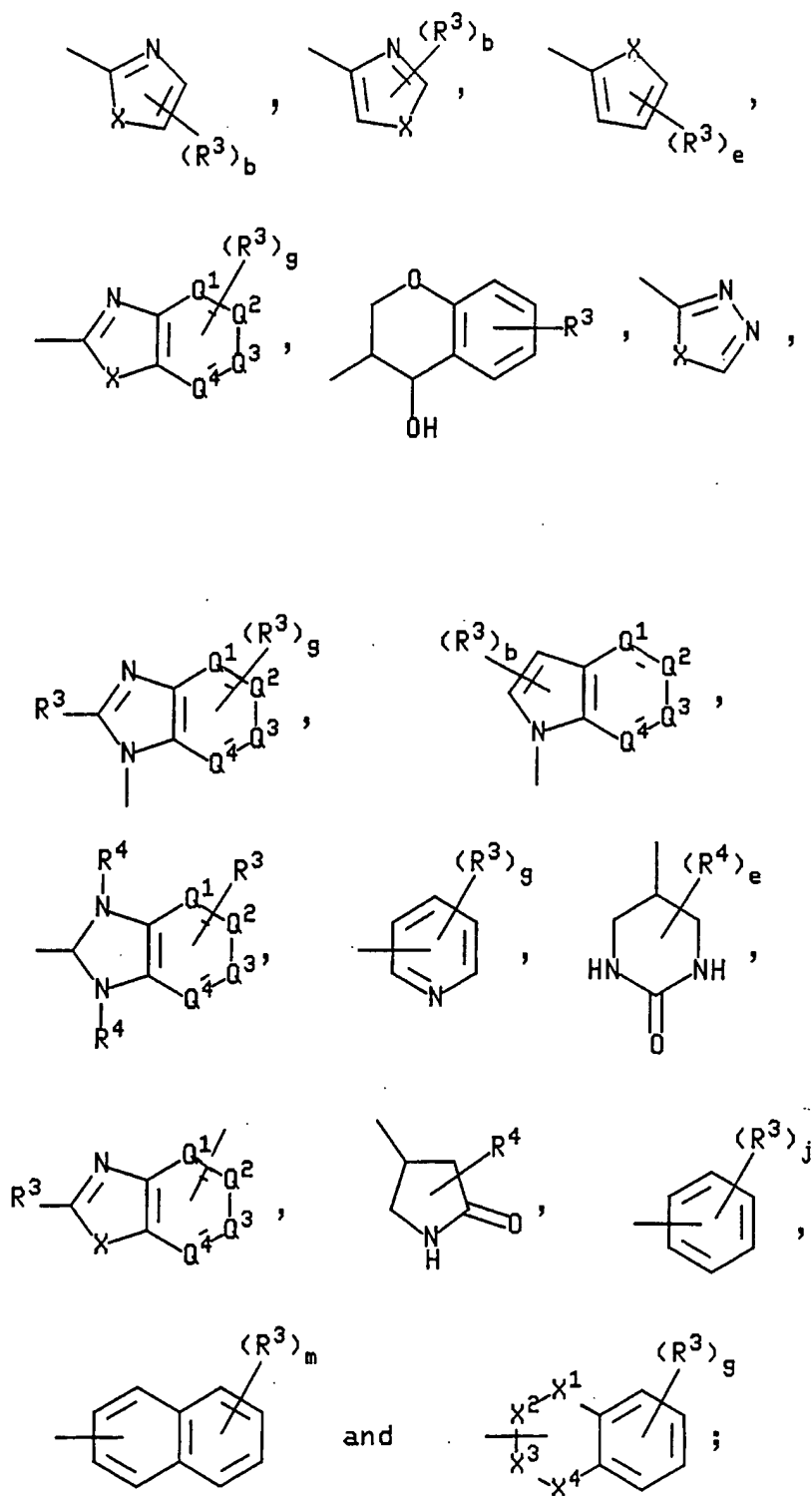
A is selected from the group consisting of a covalent bond, (C_1-C_5) alkylene and (C_2-C_5) alkenyl;

B is selected from the group consisting of a covalent bond, phenylene optionally substituted with (C_1-C_4) alkoxy, (C_1-C_5) alkylene and (C_2-C_5) alkenyl;

Y is selected from the group consisting of a covalent bond, O and NR^6 ;

Z is selected from the group consisting of

-9-



-10-

each R^3 is independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, $CH(R^7)CO_2R^4$, (C_1-C_6) alkoxy, CO_2R^4 , $CONR^4R^5$, nitro, hydroxy, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen and (C_1-C_6) alkyl,

R^5 is selected from the group consisting of hydrogen and (C_1-C_6) alkyl, and Q^1 , Q^2 , Q^3 , Q^4 , X , X^1 , X^2 , X^3 , X^4 , b , e , g , j , m , R^6 and R^8 are as defined above.

A more preferred group of compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl;

R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion;

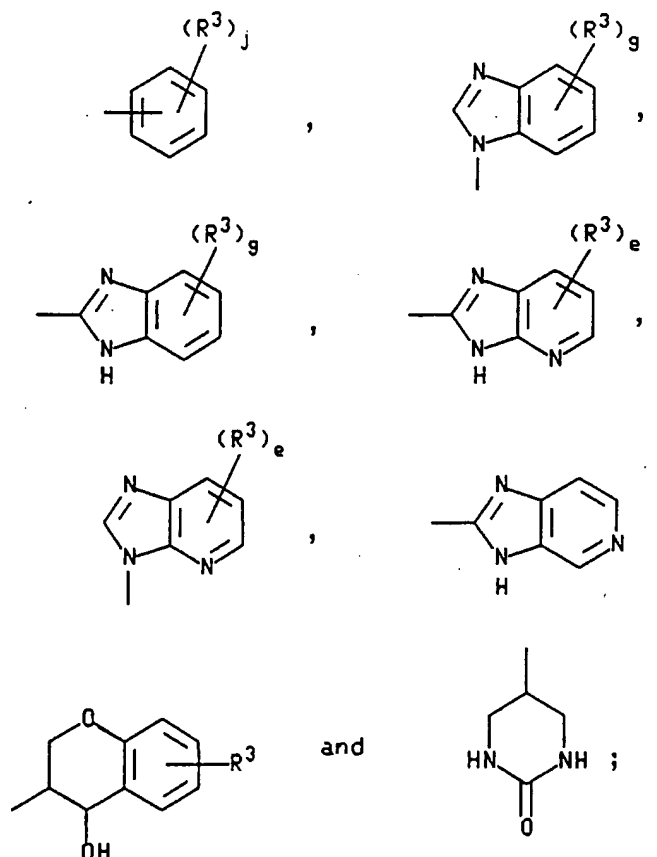
A is selected from the group consisting of a covalent bond and methylene;

B is selected from the group consisting of a covalent bond, methylene and phenylene;

Y is selected from the group consisting of a covalent bond and O;

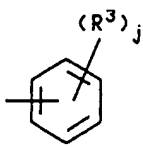
Z is selected from the group consisting of

-11-



where R^3 , e, g and j are as defined above.

Another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A, B

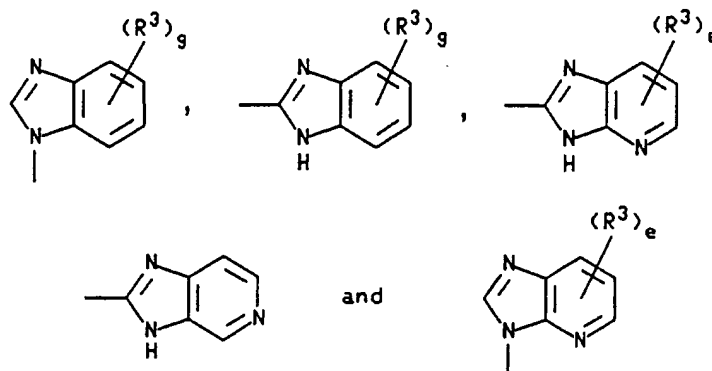
and Y are a covalent bond; and Z is , wherein R^3 and j are as defined

above for formula (I).

Another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl,

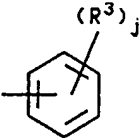
-12-

(C₆-C₉)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A, B and Y are a covalent bond; and Z is selected from the group consisting of



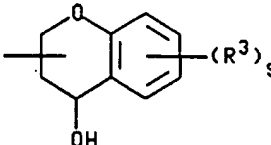
wherein R³, g and e are as defined above for formula (I).

Yet still another group of preferred compounds is that group of compounds of formula (I), above, wherein R¹ is selected from the group consisting of methyl and difluoromethyl; R² is selected from the group consisting of (C₃-C₇)cycloalkyl, (C₆-C₉)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A is

methylene; B is a covalent bond; Y is O; and Z is , wherein R³ and j are as

defined above for formula (I).

Further, another group of preferred compounds is that group of compounds of formula (I), above, wherein R¹ is selected from the group consisting of methyl and difluoromethyl; R² is selected from the group consisting of (C₃-C₇)cycloalkyl, (C₆-C₉)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A is

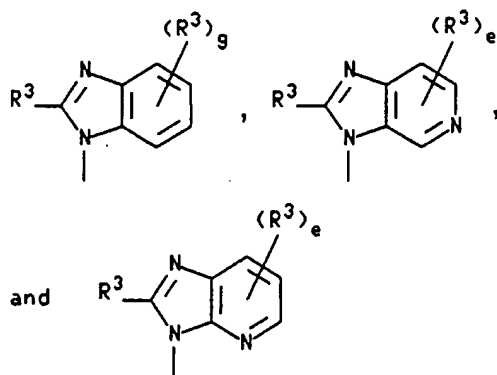
methylene; B and Y are a covalent bond; and Z is , wherein R³

and g are as defined above for formula (I).

Furthermore, another group of preferred compounds is that group of compounds of formula (I), above, wherein R¹ is selected from the group consisting of

-13-

methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion; A is methylene; B is phenylene; Y is O and Z is selected from the group consisting of



wherein R^3 , g and e are as defined above for formula (I).

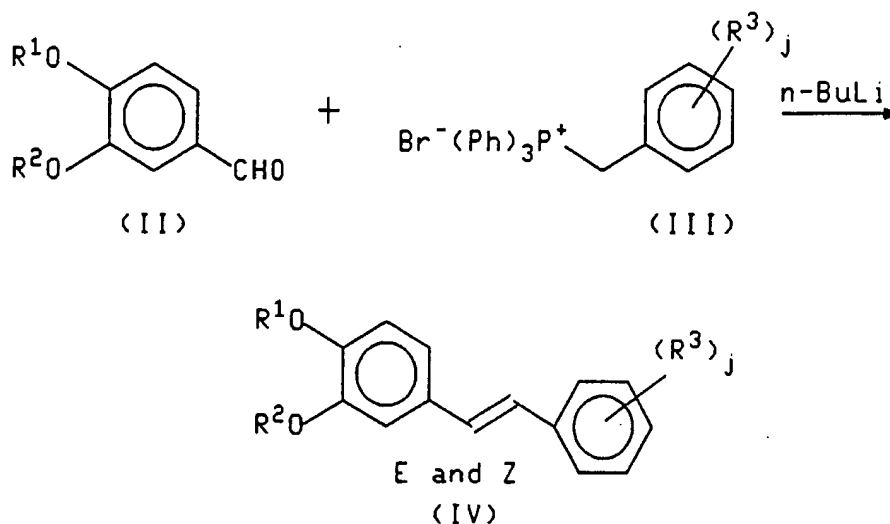
The starting materials and reagents required for the synthesis of the compounds of the present invention are readily available, either commercially, according to literature methods, or by methods exemplified in Preparations below.

Detailed Description of the Invention

The compounds of the invention can be prepared by a number of different processes according to the invention.

(a) In one process certain compounds of the formula (IV) can be prepared by the Wittig synthesis, according to the following reaction scheme:

-14-



wherein R^1 , R^2 , R^3 and j are as defined above for formula (I).

In a typical procedure, approximately one equivalent of the phenylphosphonium bromide (III), dissolved or suspended in dry THF, is treated with about 1.1 equivalents of 2.5M $n\text{-BuLi}$ in hexane. This mixture is allowed to stir at about -78°C for about one hour. Then approximately one equivalent of the aldehyde (II), dissolved in anhydrous THF, is added to the formed ylide solution at about -78°C . After about one hour of stirring at about -78°C , the reaction mixture is allowed to warm to room temperature over about 18 hours. The reaction is worked-up by pouring it into water and extracting twice with a solvent such as ethyl acetate. The ethyl acetate is evaporated and the crude product is chromatographed on silica gel using 15% ether/hexanes as the eluant to yield the desired compound (IV). Both the cis and trans isomers of (IV) are isolated.

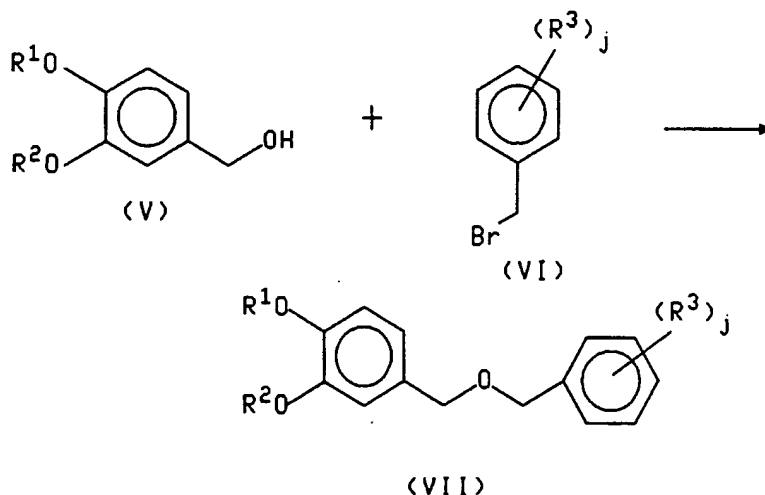
(b) In another process, a compound of the formula (IV), where j is 1 and the R^3 is either a methyl or an ethyl ester, is saponified to yield the analogous acid. In a typical procedure one equivalent of an ester of the formula (IV) is dissolved in a protic solvent, such as methanol. The ester is then mixed with about 1.5 to 10 equivalents (typically 2 equivalents) of 1N NaOH and heated at reflux temperature for about 0.5 hours to 5 hours (typically 1.5 hours). The reaction mixture is poured into water and washed once with a solvent, such as ethyl acetate. The aqueous layer is acidified to about pH 4 typically with HCl (aq) and extracted 3 times with ethyl acetate. The pure

-15-

desired product can be obtained by standard methods known to those skilled in the art such as crystallization or column chromatography on silica gel.

(c) In yet another process, a compound of the formula (IV) having the double bond can be hydrogenated to yield the corresponding alkylene analog. In a typical procedure about one equivalent of the compound (IV) is mixed with about 0.2 g to 1 g of 10% Pd/C in a mixture of protic and ether solvents, such as methanol and tetrahydrofuran. The mixture is placed in a Parr apparatus and pressurized with about 10 to 55 psi H₂, usually about 20 psi H₂, and shaken at room temperature (although the temperature may be raised as required) for about 1 to 24 hours, typically about 2 hours. The reaction mixture is filtered through celite to remove the catalyst and purified by chromatography on silica gel.

(d) In an alternative process, certain compounds of formula (VII) can be prepared by the Williamson synthesis, according to the following general reaction scheme:



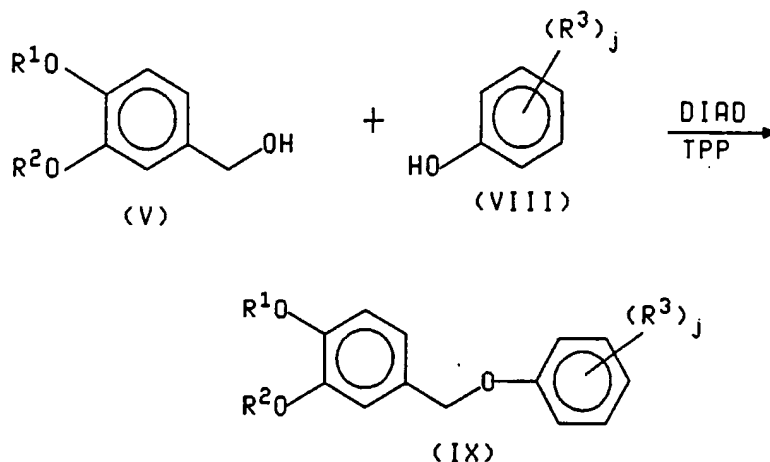
wherein R¹, R², R³ and j are as defined above for formula (I).

In a typical procedure, about 1 to 2 equivalents, typically about 1.05 equivalents, of a 60% oil dispersion of NaH is added to a solution of the alcohol of formula (V) at room temperature. The alcohol of formula (V) is usually dissolved in dry dimethylformamide. The mixture is stirred for about 0.5 to 2 hours, typically about 1 hour, at room temperature, at which time the bromo compound of formula (VI) is added. The reaction mixture is stirred and heated to 100-125°C for about 24 hours to 72 hours. The

-16-

reaction is worked-up by pouring it into water and extracting twice with ethyl acetate followed by purification by chromatography on silica gel.

(e) In a further process, certain compounds of general formula (IX) can be prepared by a Mitsunobu type reaction, according to the following general reaction scheme:

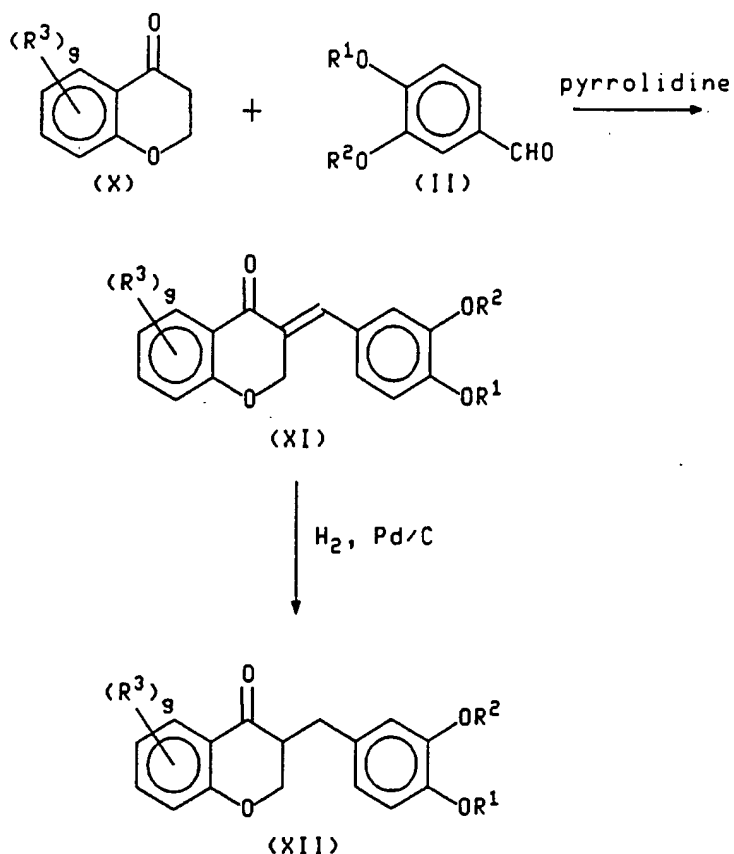


wherein R¹, R², R³ and j are as defined above for formula (I).

In a typical procedure, about 1 to 5 equivalents, typically 1.2 equivalents, of diisopropylazodicarboxylate (DIAD) or diethylazodicarboxylate (DEAD) is added to a mixture of about one equivalent of the alcohol (V), about one equivalent of the phenol (VIII) and about 1.1 equivalents of triphenylphosphine (TPP). All of the reactants are dissolved in a dry solvent, such as tetrahydrofuran. The reaction is stirred at room temperature for about 6 to 24 hours, typically 18 hours. The solvent is evaporated and the crude oil is purified by column chromatography on silica gel to yield the compound of formula (IX).

(f) In another process, certain compounds of the formula (XI) are prepared by the following general reaction scheme:

-17-



wherein R^1 , R^2 , R^3 and g are as defined above for formula (I).

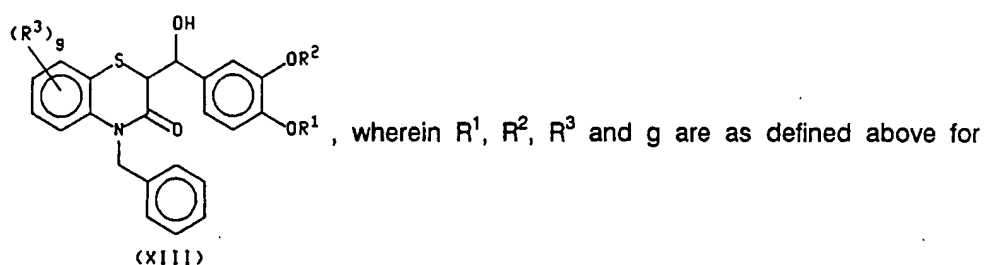
About 1 equivalent of a secondary amine base, such as pyrrolidine is added to a room temperature solution of about 1 equivalent of the appropriately substituted chromanone (X) and about 1 equivalent of the necessary aldehyde (II) in a protic solvent such as methanol. The mixture is stirred for about 6 to 24 hours, usually 18 hours. The mixture is filtered to give the desired product as a solid. The compound of formula (XI) is then purified by either crystallization or by column chromatography. The compound of formula (XII) is obtained by hydrogenating compound (XI) analogous to method (c) above.

(g) In a further process, the ketone moiety of the chromanone compound of formula (XII) described hereinabove in method (f) can be reduced to the corresponding alcohol with a reducing agent such as $NaBH_4$. Approximately 0.8 equivalents of sodium

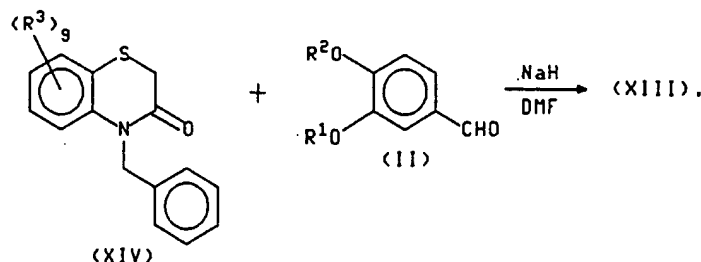
-18-

borohydride is added to a solution of approximately 1 equivalent of the chromanone (XII) and about 1 equivalent of $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$ in methanol and tetrahydrofuran. The temperature of the solution is usually about -20°C to -78°C , preferably -50°C . The reaction mixture is allowed to warm to room temperature over about 18 hours. The reaction is worked up by diluting with ethyl acetate and washing once each with NH_4Cl (aqueous), H_2O and brine. It is then dried over Na_2SO_4 and concentrated. The crude product is purified by chromatography on silica gel.

(h) Certain compounds having the general formula



formula (I), may be synthesized according to the following scheme:



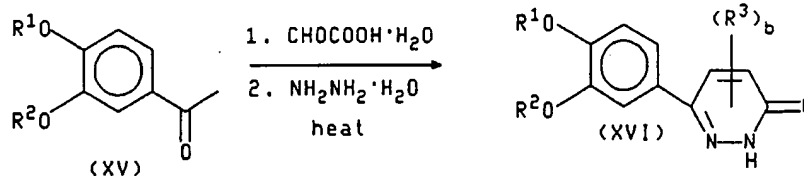
A solution of about one equivalent of (XIV) in dry DMF is added dropwise to a suspension of about 1.1 equivalents of NaH in dry DMF at about 0°C . The solution is stirred at about 0°C for about 30 minutes when a one equivalent solution of (II) in dry DMF is added. The mixture is allowed to come to room temperature over about 18 hours. The mixture is poured into water and acidified to pH 1. The resulting precipitate is filtered and dried. Further purification is done by chromatography on silica gel.

(i) In yet another process, an alcohol of formula (XIII) described in method (h), above, may be dehydrated to give the corresponding alkenyl analog. In a typical procedure, about 1.5 equivalents of oxalyl chloride is added to a solution of about 2

-19-

equivalents of dry DMSO in dry methylene chloride at about -50°C to -78°C , preferably at -65°C . A solution of the alcohol of the formula (XIII) described in method (h), above, dissolved in dry methylene chloride, is added to the cold solution of DMSO. This mixture is allowed to warm with stirring to about -30°C over about 1 hour. It is then cooled to about -78°C and 2 to 10 equivalents of triethylamine is added. This mixture is stirred at room temperature for about 1 hour. The reaction is worked-up by standard methods known to those skilled in the art and purified either by column chromatography on silica gel or by crystallization.

(j) Certain compounds of the formula (XVI) may be synthesized according to the scheme shown below:

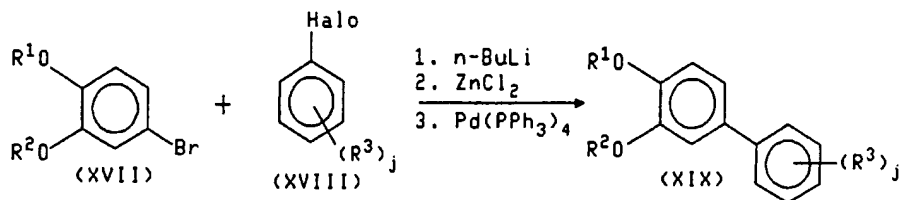


wherein R^1 , R^2 , R^3 and b are as defined above for formula (I).

In a typical procedure, a ketone of the formula (XV) is heated with glyoxylic acid monohydrate at about 100°C to 150°C , preferably about 120°C . The reaction is cooled to about 60°C and about 2 ml of H_2O is added. About 20 to 30 drops of concentrated NH_4OH and about 1 equivalent of hydrazine monohydrate are added. The mixture is then heated at reflux for about 2 hours. It is cooled to room temperature and about 5 ml of water is added. The mixture is stirred for about 50 to 72 hours, preferably for about 60 hours. The suspension is filtered and purified by column chromatography on silica gel followed by crystallization.

(k) Certain compounds of formula (XIX) are prepared by palladium cross coupling according to the following scheme:

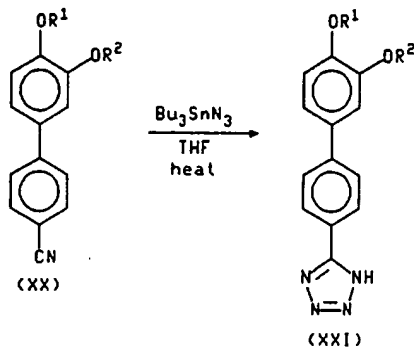
-20-



wherein R^1 , R^2 , R^3 and j are as defined above for formula (I).

A typical procedure is carried out by taking a solution of about one equivalent of the appropriate bromo compound (XVII), dissolved in dry THF, and cooling it to about -78°C . About 1.1 equivalents of a 2.5M solution of n-BuLi is added to the bromo compound and stirred for about 40 minutes at about -78°C . About 1.2 equivalents of a 1.0M solution of ZnCl_2 in ether is added and the reaction mixture allowed to warm to room temperature over about 35 minutes. A catalytic amount, about 0.05 equivalents, of tetrakis(triphenylphosphine)palladium(0) and the required halo compound (XVIII), wherein "Halo" is I, Br or Cl but preferably I or Br, are added to the reaction mixture and allowed to stir for about 12 hours. The reaction is concentrated and chromatographed on silica gel to yield the desired compound of formula (XIX).

(I) Yet another process which is utilized to prepare certain compounds of formula (I) involves the formation of a tetrazole from a cyano group using Bu_3SnN_3 , according to the general scheme:

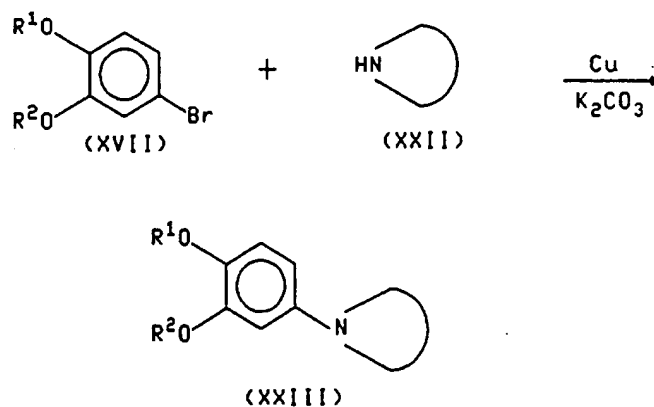


wherein R^1 and R^2 are as defined above for formula (I).

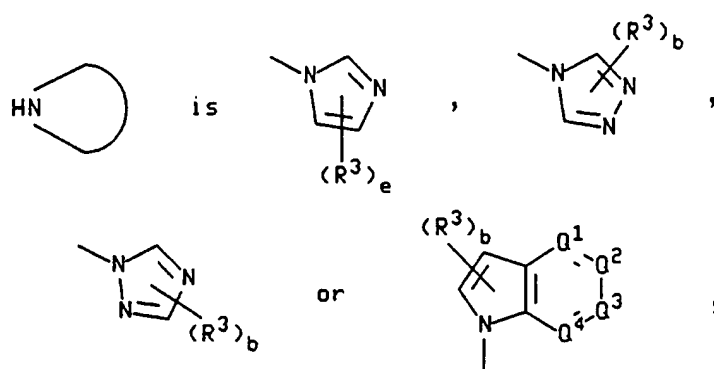
-21-

In a typical method, about one equivalent of the cyano compound of formula (XX), dissolved in dry THF, is mixed with a dry THF solution of Bu_3SnN_3 and the mixture heated at reflux temperature for about 4 days. The mixture is cooled to room temperature, concentrated and chromatographed on silica gel to afford the desired tetrazole (XXI).

(m) Certain compounds of formula (I) may also be synthesized by reaction of bromo compounds (XVII) with amino compounds (XXII), according to the general reaction scheme:



wherein R^1 and R^2 are as defined above for formula (I) and



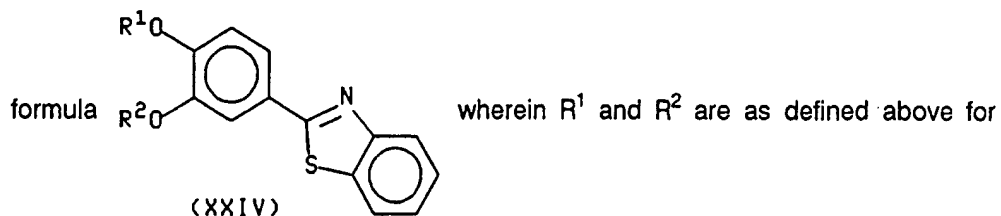
wherein Q^1 , Q^2 , Q^3 , Q^4 , R^3 , b and e are as defined above for formula (I).

In a typical procedure, a mixture of about one equivalent of all of the reagents shown in the above scheme are heated to about 110-150°C for about 24 hours. The

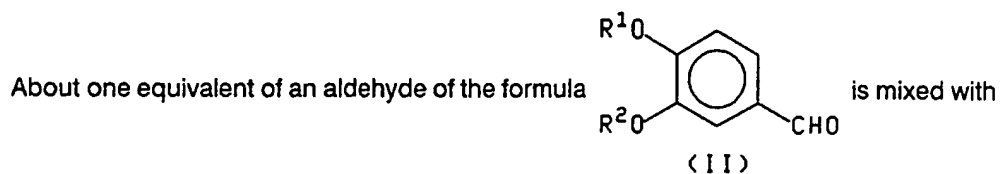
-22-

mixture is cooled to room temperature and worked-up according to standard methods well known to those skilled in the art. Chromatography on silica gel yields the desired compound of general formula (XXIII).

(n) The following procedure is employed to synthesize compounds of the



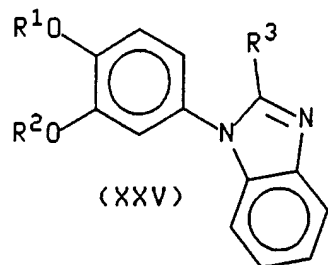
formula (I).



about one equivalent of an optionally substituted 2-mercaptoaniline and heated on a steam bath for about 15 minutes. The reaction mixture is cooled and dissolved in a methanol solution of 10% FeCl₃ and stirred overnight. The reaction is diluted with H₂O and extracted with chloroform. The chloroform is evaporated and the residue is chromatographed to yield the desired benzothiazole derivatives of formula (XXIV).

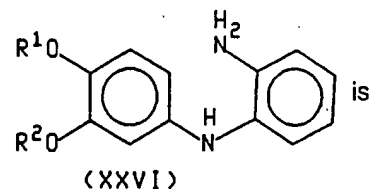
-23-

(o) The following procedure is used to synthesize compounds of the formula



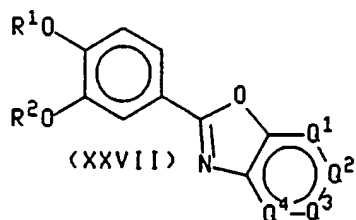
wherein R^1 , R^2 and R^3 are as defined above for formula (I).

About one equivalent of a compound of the formula



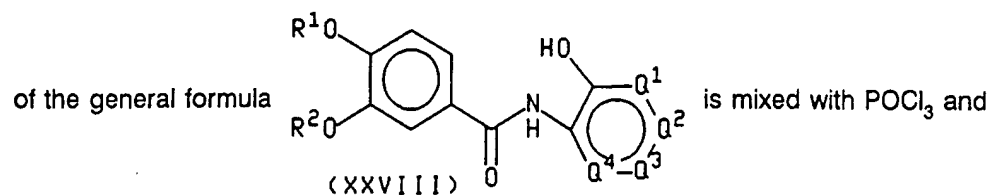
mixed with ethyl formate and approximately 25 ml of formic acid and heated at about 100°C for about 18 hours. The solvent is evaporated and the residue chromatographed on silica gel to yield the desired benzimidazole derivatives of formula (XXV).

(p) Compounds having the general formula



, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Q^4 are as defined

above for formula (I), are synthesized by the following general method. A compound

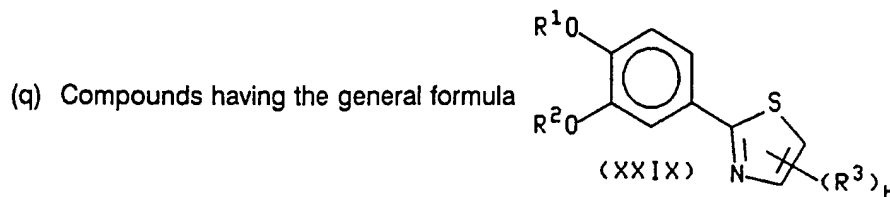


of the general formula

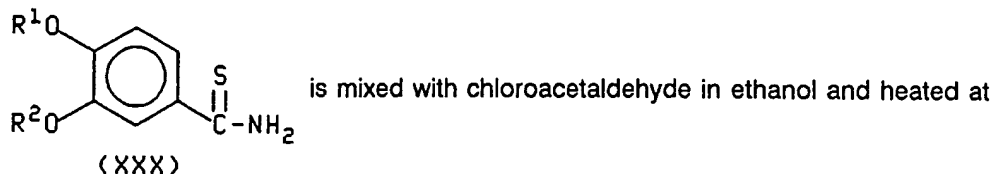
is mixed with POCl_3 and

-24-

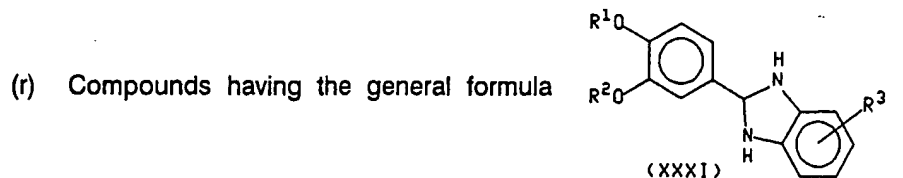
heated at reflux for about 24 hours. Excess POCl_3 is evaporated and the crude product is purified by chromatography on silica gel to yield the desired oxazolo derivatives of formula (XXVII).



wherein R^1 , R^2 , R^3 and b are as defined above for formula (I), are synthesized by the following general method. A compound of the general formula



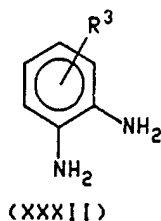
reflux temperature for about 6 hours. The volatile components are evaporated and the residue is purified by chromatography on silica gel to yield the desired thiazole derivative of formula (XXIX).



wherein R^1 , R^2 and R^3 are as defined above for formula (I), are synthesized by the following general method. A compound of the general formula (II) is mixed with an

-25-

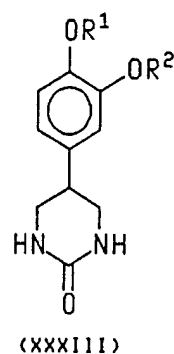
appropriate compound of the general formula



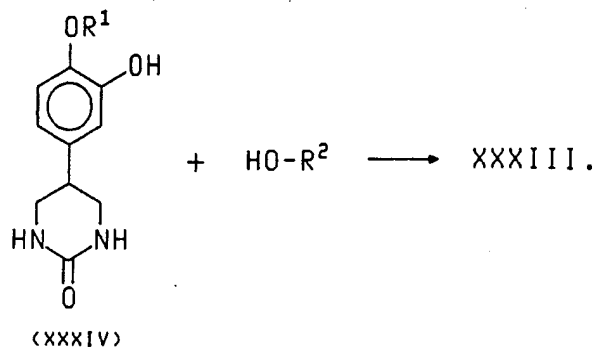
and the mixture heated

to about 120°C for about 1 to 6 hours. The resulting residue is chromatographed on silica gel to yield the desired derivative of formula (XXXI).

(s) Compounds having the general formula

, wherein R¹ and

R² are as defined above for formula (I), are synthesized by one of the two general methods described below. The first general method is a Mitsunobu type reaction illustrated by the general scheme



The reaction is carried out analogously to the description provided in general method (e) above.

The second general method is carried out according to the following general scheme: $\text{XXXIV} + \text{Halo-R}^2 \longrightarrow \text{XXXIII}$, wherein "Halo" is Cl, Br or I.

A compound of general formula (XXXIV) is dissolved in anhydrous DMSO. To this mixture approximately 2.5 equivalents of anhydrous K_2CO_3 and the appropriate halide (Halo-R^2) are added. The reaction mixture is heated to about 80°C for about 2-5 hours. After conventional work-up of the reaction mixture, the desired product is isolated by chromatography on silica gel.

The synthetic methods outlined above in methods a to s together with the following Examples describe methods which were and can be employed to prepare the compounds of this invention.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase IV (PDE_4) and, consequently, demonstrate their effectiveness for treating inflammatory diseases is shown by the following in vitro assay.

BIOLOGICAL ASSAY

(Human lung PDE_4)

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at $48,000 \times g$ for 70 minutes at 4°C . The supernatant is filtered twice through a $0.22 \mu\text{m}$ filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_4 activity, determined by $[^3\text{H}]\text{cAMP}$ hydrolysis and the ability of a known PDE_4 inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

-27-

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μ M compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

- i) 25 μ l compound or DMSO (1%, for control and blank)
- ii) 25 μ l pH 7.5 Tris buffer
- iii) [3 H]cAMP (1 μ M)
- iv) 25 μ l PDE_{IV} enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [3 H]cAMP is washed with 2 x 6 ml washing buffer, and [3 H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [3 H].

% Inhibition is determined by the formula:

$$\% \text{ Inhibition} = 1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$$

IC₅₀ is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [3 H]cAMP to [3 H]5'AMP.

Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO₃, H₂SO₄, H₃PO₄, CH₃SO₃H, p-CH₃C₆H₄SO₃H, CH₃CO₂H, gluconic acid, tartaric acid, maleic acid and succinic acid. In the case of those compounds of the formula (I) which contain a further basic nitrogen, it will, of course, be possible to form diacid addition salts (e.g., the dihydrochloride) as well as the usual monoacid addition salt. Pharmaceutically-acceptable cationic salts of the compounds of this invention include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

-28-

For administration to humans in the curative or prophylactic treatment of inflammatory conditions, oral dosages of the compounds are generally in the range of from 0.1-100 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovals either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic.

Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula (I), or pharmaceutically acceptable salts thereof, together with a pharmaceutically acceptable diluent or carrier.

This invention also provides a method of inhibiting phosphodiesterase IV (PDE_{IV}) in a mammal in need thereof which method comprises administering to said mammal a phosphodiesterase IV inhibiting amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof.

This invention further provides a method of treating an inflammatory condition in mammals which comprises administering to said mammal an antiinflammatory amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof.

Further still, this invention provides a method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis

-29-

or shock in a mammal which comprises administering to said mammal an effective amount of a compound or a pharmaceutically acceptable salt thereof.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

-30-

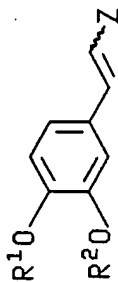
EXAMPLE 1

Methyl 3-[2-[3-(cyclopentyloxy)-
4-methoxyphenyl]ethenyl] benoate

To a -78°C suspension of (1.55 g, 3.16 mmol, 1.05 eq) 3-carbomethoxybenzyltriphenylphosphonium bromide in 50 ml of anhydrous tetrahydrofuran (1.20 ml of 2.5M, 3.01 mmol, 1.0 eq) n-BuLi in hexane was added dropwise. After stirring 45 minutes at -78°C, a solution of (0.663 g, 3.01 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxybenzaldehyde in 20 ml of anhydrous tetrahydrofuran was added dropwise, and the reaction mixture was allowed to warm to room temperature over 18 hours. The reaction mixture was poured into 300 ml H₂O and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with brine, dried over Na₂SO₄, and concentrated to yield 2.12 g of a yellow oil. Silica gel chromatography eluting with 15% ether-hexane afforded 386 mg, 36%, of the cis isomer and 380 mg, 36%, of the trans isomer. Mass spectra: M⁺ = 352.

EXAMPLES 2-3

Reaction of the appropriate aldehyde with the requisite aryltriphenylphosphonium bromide, analogous to the procedure of Example 1, afforded the following compounds having the general formula:



Ex.#	Isomer	R¹	R²	Z	M.P. °C	Analysis					
						Calculated (%)			Found (%)		
						C	H	N	C	H	N
2	Cis & Trans Mixture	CH ₃			65-67°	76.17	6.93	--	76.15	7.03	--
3	Cis & Trans Mixture	CH ₃			Oil	78.11	7.02	--	78.23	7.21	--

-32-

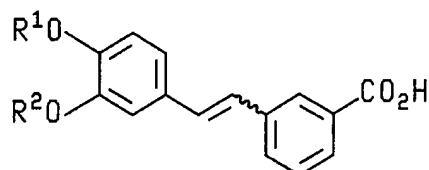
EXAMPLE 4

3-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic Acid

A mixture of (335 mg, 0.951 mmol, 1.0 eq) methyl, 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate in 8 ml methanol and 1.9 ml (1.90 mmol, 2.0 eq) of 1N NaOH was heated to reflux for 1.5 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, poured into 100 ml H₂O, basified to pH 12, and washed once with ethyl acetate. The aqueous layer was acidified to pH 4 and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed once with H₂O, once with brine, dried over Na₂SO₄, and concentrated to yield 295 mg of white waxy crystals. Recrystallization from ethyl acetate-hexane afforded 110 mg, 34%, of the cis isomer as white crystals. M.P.: 93-94°C. Elemental Analysis: Calc'd for C₂₁H₂₂O₄: Calc'd: C, 74.53; H, 6.55. Found: C, 74.32; H, 6.68.

EXAMPLES 5-6

Reaction of the appropriate methyl ester, analogous to the procedure of Example 4, afforded the following compounds:



Ex.#	Isomer	R¹	R²	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
5	Trans	CH₃		137-138°	74.53	6.55	74.27	6.39
6	Cis	CH₃		79-81°	—	—	—	—

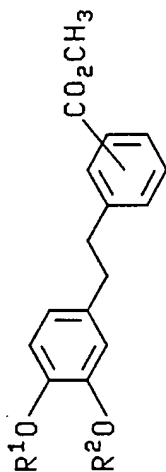
EXAMPLE 7

Methyl 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethenyl]benzoate

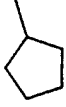

A mixture of (1.18 g, 2.74 mmol, 1.0 eq) methyl 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethenyl]benzoate and 0.600 g of 10% Pd/C in 30 ml methanol and 30 ml tetrahydrofuran was placed on a Parr hydrogenation apparatus and shaken under 20 psi H₂ at room temperature for 1.5 hours. The reaction mixture was filtered through celite, concentrated in vacuo, and flash chromatographed on a silica gel column eluting with 20% ether-hexane to afford 1.00 g, 84%, of a clear oil. Elemental Analysis Calc'd for C₂₈H₃₂O₄: Calc'd: C, 77.75; H, 7.46. Found: C, 77.55; H, 7.55.

EXAMPLES 8-10


Reaction of the appropriate alkenylaryl methyl ester, analogous to the procedure of Example 7, afforded the following compounds:



-34-

Ex.#	R ¹	R ²	Position of CO ₂ CH ₃	M.P. °C	Formula (MW)	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
8	CH ₃		meta	oil	C ₂₂ H ₂₆ O ₄ 354.4	354	--	--	--	--
9	CH ₃		meta	oil	C ₂₄ H ₂₈ O ₄ 380.4	380	75.77	7.42	75.58	7.68

-35-

Ex. #	R ¹	R ²	Position of CO ₂ CH ₃	M.P. °C	Formula (MW)	Mass Spec (M ⁺)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
10	CH ₃		para	72-74°	C ₂₄ H ₂₈ O ₄ 380.4	380	--	--	--	--

-36-

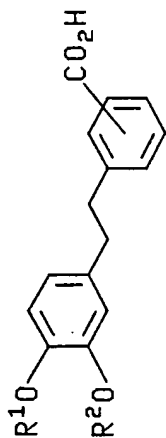
EXAMPLE 11

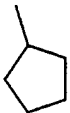
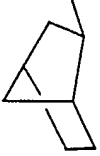
4-[2-[4-methoxy-3-(1-methyl-4-phenyl-
butoxy)phenyl]ethyl]benzoic acid

Reaction of methyl, 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethyl]-benzoate, analogous to the procedure of Example 4, yielded the title compound, 735 mg, 91%, as white crystals. M.P.: 112°C. Elemental Analysis Calc'd for $C_{27}H_{30}O_4$: Calc'd: C, 77.48; H, 7.23. Found: C, 77.62; H, 7.36.

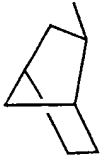
EXAMPLES 12-14

Reaction of the appropriate methyl ester, analogous to the procedure of Example 11, afforded the following compounds:



Ex. #	R¹	R²	Position of CO₂H	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
12	CH₃		meta	86-8°	74.09	7.11	74.21	7.16
13	CH₃		meta	105-7°	75.39	7.15	75.54	7.16

-38-

Ex. #	R ¹	R ²	Position of CO ₂ H	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
14	CH ₃		para	149-50°	75.39	7.15	75.20	7.13

-39-

EXAMPLE 15

3-[[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]methyl]benzoic acid

Added (178 mg, 4.44 mol, 1.05 eq) 60% NaH to a room temperature solution of (1.05 g, 4.23 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenylmethanol in 20 ml anhydrous dimethylformamide. After stirring 45 minutes at room temperature, (1.45 g, 6.35 mmol, 1.5 eq) of methyl-3-bromomethylbenzoate was added. After 60 hours at room temperature, the reaction mixture was poured into 300 ml H₂O and extracted twice with ethyl acetate. The ethyl acetate extracts were washed twice with H₂O, once with brine, dried over Na₂SO₄, and concentrated to yield 2.33 g of a yellow oil. Silica gel chromatography eluting with 10%, then 20% ethyl acetate-hexane afforded 322 mg, 19%, of a colorless oil, methyl, 3-[[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]methyl]benzoate.

A mixture of (310 mg, 0.782 mmol, 1.0 eq) the above methyl ester (the colorless oil) in 10 ml methanol and 3 ml of 1N NaOH was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, poured into 150 ml H₂O and 25 ml ethyl acetate, acidified to pH 4.5, and extracted twice with ethyl acetate. The ethyl acetate extracts were washed once with H₂O, once with brine, dried over Na₂SO₄, and concentrated to yield 0.28 g of a pale yellow oil. Silica gel chromatography, eluting with 5% CH₃OH-CH₂Cl₂, followed by recrystallization from ether/petroleum ether afforded 217 mg, 73%, of white crystals. M.P.: 77-79°C. Elemental Analysis: Calc'd for C₂₃H₂₆O₅: Calc'd: C, 72.31; H, 6.86. Found: C, 72.30; H, 6.80.

EXAMPLE 16

2-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenylmethoxy]nicotinic acid

A mixture of (0.82 g, 3.3 mmol, 1.0 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (0.263 g, 6.6 mmol, 2.0 eq) NaH (60% oil dispersion) in 20 ml of anhydrous dimethylformamide was stirred at room temperature for 0.5 hours. 2-Chloronicotinic acid (0.52 g, 3.3 mmol, 1.0 eq) was added, and the reaction mixture heated to reflux for 24 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, dissolved in ethyl acetate and washed with 2N NaOH. The base wash was acidified to pH 5-6 and extracted with ethyl acetate. The ethyl acetate extracts were washed twice with H₂O, once with brine, dried over Na₂SO₄ and concentrated to yield

-40-

944 mg of a white semi-solid. Silica gel chromatography eluting with 2½%, then 4% CH₃OH-CH₂Cl₂ afforded 69 mg, 6%, of a white amorphous foam. M.P.: 50°C+(dec.).

EXAMPLE 17

6-[[3-(Bicyclo[2.2.1]-hept-2-yloxy)-4-methoxy-phenyl]methoxy]- α -methyl-2-naphthaleneacetic acid

(\pm)-3-Exo-norbornyloxy-4-methoxybenzyl bromide (0.719 g, 2.31 mmol, 1.0 eq) was added to a mixture of (0.50 g, 2.31 mmol, 1.0 eq) α -methyl-2-(5-hydroxynaphthalene acetic acid and (1.12 g, 3.5 eq, 8.09 mmol) K₂CO₃ in 35 ml of anhydrous dimethylformamide. After stirring 18 hours at room temperature under N₂, the reaction mixture was poured into 350 ml of H₂O, acidified to pH 4-5 and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H₂O, once with brine, dried over Na₂SO₄, and concentrated in vacuo to yield a yellow-brown oil. Silica gel chromatography eluting with 2½% CH₃OH-CH₂Cl₂ gave 0.52 g of a white amorphous solid. Recrystallization from isopropanol-hexane yielded 0.47 g, 46%, of a light yellow crystal. M.P.: 125-128°C. Elemental Analysis: Calc'd for C₂₈H₃₀O₅: Calc'd: C, 75.31; H, 6.77. Found: C, 75.26; H, 7.01.

EXAMPLE 18

Methyl 3-[[3-(cyclopentyloxy)-4-methoxyphenyl]methoxy]benzoate

Diisopropylazodicarboxylate (1.2 ml, 5.99 mmol, 1.2 eq) was added to a mixture of (1.10 g, 4.99 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxybenzyl alcohol, (1.44 g, 5.49 mmol, 1.1 eq) triphenylphosphine, and (0.75 g, 4.99 mmol, 1.0 eq) methyl-3-hydroxybenzoate in 30 ml of anhydrous tetrahydrofuran. After stirring for 18 hours at room temperature the reaction mixture was concentrated in vacuo and chromatographed on a silica gel column, eluting with 10%, then 15% ethyl acetate-hexane to yield 897 mg, 50%, of a clear oil. High Resolution Mass Spectra: Calc'd 356.1624. Found: 356.1600.

EXAMPLE 19

Tetrahydro-5-[4-methoxy-3-(difluoromethoxy)phenyl]-2(1H)-pyrimidinone

Chlorodifluoromethane was bubbled into a solution of (102 mg, 0.459 mmol, 1.0 eq) of tetrahydro-5-(4-methoxy-3-hydroxyphenyl)-2(1H)-pyrimidinone and 64 mg (1.61 mmol, 3.5 eq) of NaOH in 3 ml of H₂O and 3 ml of 1,4-dioxane. After 1 hour at room temperature, the reaction mixture was heated to 60°C for 1.5 hours. Chlorodifluoromethane was bubbled in continuously. The reaction mixture was cooled to room

-41-

temperature, poured into 150 ml of H₂O and 75 ml of ethyl acetate, extracted twice with ethyl acetate. The ethyl acetate extracts were washed twice with 2N NaOH, once with brine, dried over Na₂SO₄, and concentrated to yield 13.5 mg of a white solid, which was recrystallized from ethyl acetate-hexane to afford 8.4 mg, 7%, of off-white crystals. M.P.: 215-216°C. Elemental Analysis: Calc'd for C₁₂H₁₄N₂O₃F₂: Calc'd: C, 52.95; H, 5.18; N, 10.29. Found: C, 52.88; H, 4.91; N, 10.13.

EXAMPLE 20

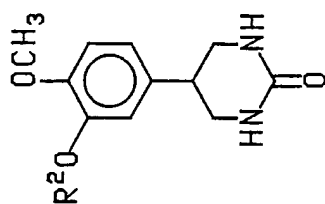
5-(3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxyphenyl)tetrahydro-2(1H)-pyrimidone

Pb(OAc)₄ (2.96 g of 95%, 6.67 mmol, 2.2 eq) was added portionwise to a slurry of (1.16 g, 3.03 mmol, 1.0 eq) 3-[3-bicyclo[2.2.1]hept-2-yloxy)-4-(difluoromethoxy)-phenyl]pentanediamide, in 50 ml anhydrous pyridine. After stirring 18 hours at room temperature, the reaction mixture was poured into 600 ml of H₂O and extracted four times with ethyl acetate. The ethyl acetate extracts were washed once with brine, dried over Na₂SO₄, and concentrated to yield 1.4 g of a yellow solid. Silica gel chromatography eluting with 2½%, then 3% CH₃OH-CH₂Cl₂ yielded 1.06 g of a white solid. Recrystallization from ethyl acetate-hexane afforded 598 mg, 56%, of white crystals. M.P.: 217-219°C. Elemental Analysis Calc'd for C₁₈H₂₂N₂O₃F₂: Calc'd: C, 61.35; H, 6.29; N, 7.95. Found: C, 61.53; H, 6.38; N, 7.81.

EXAMPLE 21





Tetrahydro-5-[3-(4-phenylbutoxy)-4-methoxyphenyl]-2(1H)-pyrimidinone

Diisopropylazodicarboxylate (1.1 ml, 5.70 mmol, 1.2 eq) was added to a mixture of (1.06 g, 4.75 mmol, 1.0 eq) tetrahydro-5-(3-hydroxy-4-methoxyphenyl)-2(1H)-pyrimidinone, (1.37 g, 5.23 mmol, 1.1 eq) triphenylphosphine, and (714 mg, 4.75 mmol, 1.0 eq) 4-phenyl-1-butanol in 20 ml of anhydrous tetrahydrofuran. After heating to reflux for 18 hours, the reaction mixture was cooled to room temperature, diluted with 350 ml ethyl acetate, washed twice with 1N NaOH, once with H₂O, once with brine, dried over Na₂SO₄, and concentrated to yield an orange solid. Silica gel chromatography eluting with 4% CH₃OH-CH₂Cl₂ yielded 527 mg of a white solid, which was recrystallized from ethyl acetate to afford 480 mg, 29%, of white needles. M.P.: 142-143°C. Elemental Analysis Calc'd for C₂₁H₂₆N₂O₃: Calc'd: C, 71.17; H, 7.40; N, 7.90. Found: C, 71.12; H, 7.32; N, 7.75.

EXAMPLES 22-27

Reaction of 2(1H)-pyrimidine, tetrahydro-5-(3-hydroxy-4-methoxyphenyl)- with the appropriate alcohol of the general formula R-OH, analogous to the procedure of Example 21, yielded the following compounds:

Ex. #	R ²	M.P. °C	Analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
22		157-60°	69.01	7.13	6.19	67.58	6.76	6.33
23		152-4°	71.17	7.40	7.90	71.13	7.42	7.80

Ex. #	R ²	M.P. °C	Analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
24		99-101°	--	--	--	--	--	--
25		147-9°	--	--	--	--	--	--
26		160-2°	71.72	7.66	7.60	71.17	7.49	7.48
27		90-2°	72.22	7.91	7.32	72.20	7.79	7.27

-44-

EXAMPLE 28

5-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]tetrahydro-1,3-bis(2-quinolinylmethyl)-2(1H)-pyrimidinone

NaH (63 mg, 1.58 mmol, 1.0 eq, 60% oil dispersion) was added to a mixture of (0.500 g, 1.58 mmol, 1.0 eq) 5-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]tetrahydro-2(1H)-pyrimidinone and (0.279 g, 1.58 mmol, 1.0 eq) 2-chloromethylquinoline in 12 ml of anhydrous dimethylformamide. After stirring for 18 hours at room temperature, the reaction mixture was diluted with 250 ml of H₂O and extracted with ethyl acetate. The ethyl acetate extract was washed once with H₂O, once with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on a silica gel column, eluting with 2½% CH₃OH-CH₂Cl₂ to yield 50 mg of a solid, which was recrystallized from ethyl acetate-hexane to afford 45 mg, 5%, of a white crystalline solid. M.P.: 135-136°C.

EXAMPLE 29

1-[(7-Chloro-2-quinolinyl)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone

4-[3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone (1.00 g, 3.63 mmol, 1.0 eq) was added to a room temperature suspension of (145 mg, 3.63 mmol, 1.0 eq) NaH (60% oil dispersion) in 30 ml of anhydrous DMF. After stirring at room temperature for 1 hour, (0.77 g, 3.63 mmol, 1.0 eq) 2-chloromethyl-7-chloroquinoline was added, and the reaction mixture was allowed to stir at room temperature for 60 hours. The reaction mixture was then diluted with 250 mL H₂O and extracted with ethyl acetate. The ethyl acetate extract was washed twice with H₂O, once with brine, dried over Na₂SO₄ and concentrated to yield a yellow oil. Silica gel chromatography eluting with 5% CH₃OH/CH₂Cl₂ followed by recrystallization from ethyl acetate-hexane yielded 0.61 g, 37%, of white crystals. M.P.: 106-107°C. Elemental Analysis Calc'd for C₂₈H₂₇N₂O₃Cl: Calc'd: C, 69.15; H, 6.03; N, 6.21. Found: C, 69.22; H, 5.75; N, 6.15.

EXAMPLE 30

1-(6-Fluoroquinolin-2-ylmethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidinone

Reaction of 4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidinone with 2-chloromethyl-6-fluoroquinoline, analogous to the procedure of Example 29, yielded the title compound. M.P.: 65-68°C. High Resolution Mass Spectra: Calc'd: 434.1983. Found: 434.2005.

-45-

EXAMPLE 31

[(3-Benzoic acid)methyl-4-(3-cyclopentyl-
oxy)-4-methoxyphenyl]-2-pyrrolidinone

NaH (145 mg, 3.63 mmol, 1.0 eq, 60% oil dispersion) was added to a room temperature solution of (1.00 g, 3.63 mmol, 1.0 eq) of [3-(cyclopentyl-oxy)-4-methoxy-phenyl]pyrrolidinone in 20 ml of anhydrous DMF. After stirring 45 minutes at room temperature, (832 mg, 3.63 mmol, 1.0 eq) methyl-3-bromomethylbenzoate was added. After 60 hours at room temperature, the reaction mixture was diluted with 200 ml H₂O and extracted with 200 ml of ethyl acetate. The ethyl acetate extract was washed twice with H₂O, once with brine, dried over Na₂SO₄, and concentrated in vacuo to yield a light yellow oil. Silica gel chromatography eluting with 10%, then 20% ethyl acetate-CH₂Cl₂ yielded 0.33 g, 21%, of a clear oil.

A mixture (0.33 g, 0.78 mmol, 1.0 eq) of the above methyl ester in 8.0 ml of methanol and 2.0 ml of 1N NaOH was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, diluted with H₂O, acidified to pH 4.5, and extracted with 2 x 200 ml ethyl acetate. The ethyl acetate extracts were combined, washed once with brine, dried over Na₂SO₄, and concentrated to give 300 mg of a white foamy solid. Recrystallization from ethyl acetate-hexane yielded 271 mg, 85%, of white crystals. M.P.: 110-113°C.

EXAMPLE 32

3-[2-[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-
methenyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one

Pyrrolidine (470 μ l, 5.61 mmol, 1.0 eq) was added to a room temperature solution of (1.00 g, 5.61 mmol, 1.0 eq) 6-methoxychromanone and (1.38 g, 5.61 mmol, 1.0 eq) of 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy benzaldehyde in 25 ml of methanol. After stirring 18 hours at room temperature, the reaction mixture was filtered, and the filtrant washed with methanol twice to yield 1.76 g, 77%, of a yellow powder. M.P.: 82-85°C. Elemental Analysis Calc'd for C₂₅H₂₆O₅: Calc'd: C, 73.86; H, 6.45. Found: C, 73.85; H, 6.33.

EXAMPLE 33

3-[2-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-
methenyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one

A mixture of (1.40 g, 3.44 mmol, 1.0 eq) 3-[2-[3-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methenyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one and 600 mg of 10% Pd/C in 15 ml ethyl acetate and 15 ml tetrahydrofuran was placed on a Parr

-46-

Hydrogenator and shaken under 40 psi H₂ at room temperature for 2 hours. The reaction mixture was filtered through celite, and concentrated *in vacuo* to yield 1.78 g of a pale yellow oil. Silica gel chromatography eluting with CH₂Cl₂ afforded 963 mg, 68%, of a clear oil. High Resolution Mass Spectra: Calc'd: 408.1937. Found: 408.1937.

EXAMPLE 34

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-methyl]-3,4-dihydro-6-methoxy-2H-1-benzopyran-4-ol

Sodium borohydride (59 mg, 1.57 mmol, 0.8 eq) was added to a -50°C solution of (800 mg, 1.96 mmol, 1.0 eq) 3-[2-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-ethyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one and (730 mg, 1.96 mmol, 1.0 eq) CeCl₃ · 7H₂O in 20 ml of methanol and 7 ml of tetrahydrofuran. The reaction mixture was allowed to warm to room temperature over 18 hours. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate, washed once with NH₄Cl (aq.), once with H₂O, once with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column eluting with 15% ethyl acetate-hexane, to yield 688 mg of a white amorphous foam. Recrystallization from ethyl acetate-hexane yielded 593 mg, 74%, of white crystals. M.P.: 115-117°C. Elemental Analysis Calc'd for C₂₅H₃₀O₅: Calc'd: C, 73.14; H, 7.37. Found: C, 73.35; H, 7.39.

EXAMPLE 35

2-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]- α -hydroxy-methyl]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one

A solution of (1.04 g, 4.06 mmol, 1.0 eq) 4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one in 10 ml of dry dimethylformamide was added dropwise to a 0°C suspension of (179 mg, 4.47 mmol, 1.1 eq) NaH (60% oil dispersion) in 5 ml of anhydrous dimethylformamide. After stirring at 0°C for 30 minutes, a solution of (1.00 g, 4.06 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde in 10 ml of dry dimethylformamide was added dropwise. The reaction mixture was allowed to come to room temperature over 18 hours, then it was poured into 1L of H₂O, acidified to pH 1, and the resulting precipitate filtered and dried to yield 2 g of a yellow solid. Silica gel chromatography eluting with 2.5% CH₃OH/CH₂Cl₂ followed by recrystallization from ether-hexane yielded 440 mg, 22%, of yellow crystals. M.P.: 159-161°C. Elemental Analysis Calc'd for C₃₀H₃₁NO₄S: Calc'd: C, 71.83; H, 6.23; N, 2.79. Found: C, 71.89; H, 6.43; N, 2.81.

-47-

EXAMPLE 36

2-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-
methylene]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one

To a stirred solution of (87 μ l, 1.24 mmol, 2.0 eq) dry dimethylsulfoxide in 3 ml of dry CH_2Cl_2 at -65°C was added (0.46 ml, 0.927 mmol, 1.5 eq) of 2.0M oxalyl chloride in CH_2Cl_2 . The mixture was stirred at ca. -60°C for 15 minutes, then a solution of (310 mg, 0.618 mmol, 1.0 eq) 2-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]hydroxy-methyl]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one in 10 ml dry CH_2Cl_2 was added dropwise at -65°C . The mixture was allowed to warm to -30°C over 1 hour, then cooled to -78°C and (0.43 ml, 3.09 mmol, 5.0 eq) triethylamine was added to the mixture. The mixture was stirred at room temperature for 1 hour then diluted with 400 ml ethyl acetate, washed twice with H_2O , once with brine, dried over MgSO_4 , and concentrated to give 0.3 g of an oil. Silica gel chromatography eluting with 10% ethyl acetate-hexane gave 120 mg of a yellow oil, which was recrystallized from ether-hexane to yield 55 mg, 18%, of a yellow solid. M.P.: $135\text{--}137^\circ\text{C}$. Elemental Analysis Calc'd for $\text{C}_{30}\text{H}_{29}\text{NO}_3\text{S}$: Calc'd: C, 74.51; H, 6.04; N, 2.90. Found: C, 74.53; H, 5.48; N, 2.88.

EXAMPLE 37

6-[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxyphenyl]-3(2H)-pyridazinone

A mixture of 3-Exo-(\pm)-norbornyloxy-4-methoxyacetophenone (0.88 g, 3.38 mmol, 1.0 eq) and (0.30 g, 3.29 mmol, 0.95 eq) glyoxylic acid monohydrate was heated to 120°C for 2.2 hours. The light yellow melt was cooled to 60°C and 2.0 ml of H_2O was added. Dissolution was brought on by addition of 25 drops of concentrated NH_4OH . Hydrazine monohydrate (0.163 g, 3.29 mmol, 0.95 eq) was added and the reaction mixture heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, 5 ml of H_2O was added to it, and the mixture stirred for 60 hours at room temperature. The resulting suspension was filtered, washed with H_2O and air dried to yield 0.87 g of a creamy yellow solid. Silica gel chromatography eluting with 5% $\text{CH}_3\text{OH}\text{--}\text{CH}_2\text{Cl}_2$, followed by recrystallization from isopropanol-hexane gave 0.50 g, 49%, of off-white crystals. M.P.: $188\text{--}189^\circ\text{C}$. Elemental Analysis Calc'd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: Calc'd: C, 69.21; H, 6.45; N, 8.95. Found: C, 68.92; H, 6.42; N, 8.88.

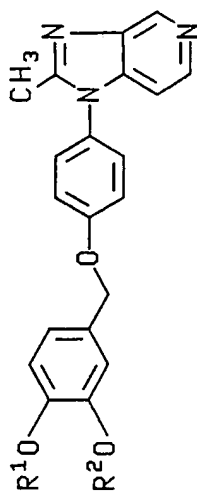
EXAMPLE 38

1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-(difluoromethoxy)-phenyl]methoxy]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

Diethylazodicarboxylate (59 μ l, 0.380 mmol, 1.2 eq) was added to a room temperature mixture of (90 mg, 0.317 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-trifluoromethoxybenzaldehyde, (78 mg, 0.348 mmol, 1.1 eq) 4-(2-methyl-1H-imidazo[4.5-c]pyrimidin-3-yl)phenol and (91 mg, 0.348 mmol, 1.1 eq) triphenylphosphine in 5 ml dry tetrahydrofuran. After stirring 18 hours at room temperature, the reaction mixture was diluted with 200 ml of ethyl acetate and washed once with 1N NaOH, once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 0.2 g of an oil. Flash chromatography on silica gel eluting with 5% CH₃OH/CH₂Cl₂ gave 85 mg of an oil, which was crystallized from ether/hexane to give 69 mg, 45%, of white crystals. M.P.: 140-141°C. Elemental Analysis: Calc'd for C₂₈H₂₇F₂N₃O₃: Calc'd: C, 68.42; H, 5.54; N, 8.55. Found: C, 68.56; H, 5.38; N, 8.53.

EXAMPLES 39-40

Reaction of the appropriate catechol with 4-(2-methyl-1H-imidazo[4,5-c]pyrimidin-3-yl)phenol, analogous to the procedure of Example 38, yielded the following compounds:



Ex. #	R¹	R²	M.P.:°C	Analysis					
				Calculated (%)			Found (%)		
				C	H	N	C	H	N
39	CH₃		122-4°	75.47	6.56	9.43	73.56	6.27	9.03
40	CH₃		151-3°	72.71	6.34	9.78	72.05	6.35	9.16

-50-

EXAMPLE 41

1-[4-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
ethenyl]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

To a stirred suspension of (1.74 g, 3.13 mmol, 1.2 eq) [[3-(cyclopentyloxy)-4-methoxyphenyl]methyl]triphenylphosphonium bromide in 20 ml dry tetrahydrofuran at -50°C was added (1.1 ml, 2.78 mmol, 1.1 eq) of 2.5M n-BuLi. The mixture was warmed to 0°C over 1 hour, cooled to -78°C, and a solution of (600 mg, 2.53 mmol, 1.0 eq) 4-(2-methyl-1H-imidazo[4,5-c]pyridin-1-yl)benzaldehyde in 20 ml dry tetrahydrofuran was added dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature over 18 hours then was quenched with 10 ml saturated NH₄Cl solution. The mixture was poured into 200 ml of H₂O and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H₂O, once with brine, dried over MgSO₄, and concentrated to give 2 g of an oil. Flash chromatography eluting with 65% acetone-hexane gave 403 mg of crude product, which was recrystallized from ether-hexane to yield 305 mg, 36%, of the cis product. The trans product was isolated from the chromatography yielding 476 mg, and crystallized from isopropylether to give 415 mg, 39%. Cis-product M.P.: 123-125°C. Trans-Product M.P.: 156-158°C. Elemental Analysis of the cis-product: Calc'd for C₂₇H₂₇N₃O₂: Calc'd: C, 76.21; H, 6.40; N, 9.87. Found: C, 76.14; H, 6.34; N, 9.71.

EXAMPLE 42

1-[4-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
ethyl]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

A cis and trans mixture of 1-[4-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]-ethenyl]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine (300 mg, 0.705 mmol 1.0 eq) and 300 mg of 10% Pd/C in 10 ml of tetrahydrofuran and 10 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H₂ at room temperature for 6 hours. The reaction mixture was filtered through celite, concentrated, and chromatographed on a silica gel column eluting with 5% CH₃OH-CH₂Cl₂ to give 230 mg of clear oil. Recrystallization from ether-hexane gave 239 mg, 79%, of white crystals. M.P.: 123-125°C. Elemental Analysis Calc'd for C₂₇H₂₉N₃O₂: Calc'd: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.83; H, 6.74; N, 9.65.

-51-

EXAMPLE 43

Methyl 1-[4-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxyphenyl]-2-butyl-1H-benzimidazole-5-carboxylate

Diethylazodicarboxylate (201 μ L, 1.28 mmol, 1.3 eq) was added to a mixture of (320 mg, 0.986 mmol, 1.0 eq) methyl 2-butyl-1-(4-hydroxyphenyl)-1H-benzimidazole-5-carboxylate, (269 mg, 1.08 mmol, 1.1 eq) (\pm)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (310 mg, 1.18 mmol, 1.2 eq) of triphenylphosphine in 10 ml of dry tetrahydrofuran at room temperature. The reaction mixture was stirred at room temperature for 18 hours, diluted with 300 ml of ethyl acetate and washed twice with 1N NaOH, once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 0.7 g of an oil. Silica gel chromatography eluting with 35% ethyl acetate/hexane gave 298 mg, 54%, of an off-white foam. Mass Spectra: Calc'd for C₃₄H₃₈N₂O₅: 554.7. Found: 554.

EXAMPLE 44

1-[4-[[3-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]phenyl-2-butyl-1H-benzimidazole-5-carboxylic acid

Reaction of (260 mg, 0.469 mmol, 1.0 eq) methyl 1-[4-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]phenyl]-2-butyl-1H-benzimidazole-5-carboxylate, (2.3 ml, 2.3 mmol, 5.0 eq) substantially according to the procedure of Example 4 yielded the title compound, 178 mg, 70%, as a white solid. M.P.: 209-211°C. Elemental Analysis Calc'd for C₃₃H₃₅N₂O₅: Calc'd: C, 73.31; H, 6.71; N, 5.18. Found: C, 72.92; H, 6.74; N, 4.94.

EXAMPLE 45

1-[4-[[3-(Bicyclo[2.2.1]-hept-2-yloxy-4-methoxyphenyl)-methoxy]phenyl]-2-butyl-1H-imidazo[4,5-c]pyridine

Diethylazodicarboxylate (441 μ L, 2.56 mmol, 1.2 eq) was added to a mixture of (570 mg, 2.13 mmol, 1.0 eq) 4-[3H-imidazo[4,5-b]-2-butyl pyridine]phenol, (582 mg, 2.35 mmol, 1.1 eq) (\pm)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (616 mg, 2.35 mmol, 1.1 eq) of triphenylphosphine in 25 ml tetrahydrofuran at room temperature. After stirring at room temperature for 60 hours, the reaction mixture was diluted with 400 ml ethyl acetate, washed once with 1N NaOH, once with H₂O, once with brine, dried over MgSO₄, and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 5% CH₃OH/CH₂Cl₂, followed by recrystallization from ether/hexane gave 328

-52-

mg, 31%, of a solid. M.P.: 123-125°C. Elemental Analysis Calc'd for $C_{31}H_{35}N_3O_3$: Calc'd: C, 74.97; H, 6.90; N, 8.46. Found: C, 74.63; H, 7.12; N, 8.29.

EXAMPLE 46

1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-
4-difluoromethoxyphenyl]methoxy]phenyl]-
2-butyl-2H-imidazo[4,5-c]pyridine

Reaction of (\pm)-3-exo-norbornyloxy-4-difluoromethoxybenzyl alcohol with 4-3H-imidazo[4,5-b]-2-butylpyridine phenol, analogous to the procedure of Example 45, yielded the above-identified compound. M.P.: 129-131°C. Elemental Analysis Calc'd for $C_{31}H_{33}F_2N_3O_3$: Calc'd: C, 69.78; H, 6.23; N, 7.82. Found: C, 69.66; H, 6.13; N, 7.82.

EXAMPLE 47

3-[4-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxyphenyl]methoxy]phenyl]-
2-butyl-3H-imidazo[4,5-b]pyridine

Diethylazodicarboxylate (365 μ l, 2.11 mmol, 1.2 eq) was added to a mixture of (470 mg, 1.76 mmol, 1.0 eq) 4-(2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenol, (480 mg, 1.93 mmol, 1.1 eq) (\pm)-3-exo-norbornyloxy-4-methoxybenzyl alcohol, and (506 mg, 1.93 mmol, 1.0 eq) triphenylphosphine in 20 ml of dry tetrahydrofuran. After stirring at room temperature for 60 hours, the reaction mixture was diluted with 400 ml of ethyl acetate, washed twice with 1N NaOH, once with H_2O , once with brine, dried over $MgSO_4$ and concentrated to give 0.8 g of an oil. Silica gel chromatography eluting with 60% ethyl acetate/hexane, followed by recrystallization from ether/hexane gave 195 mg, 24%, of tan crystals. M.P.: 130-132°C. Elemental Analysis Calc'd for $C_{31}H_{35}N_3O_3$: Calc'd: C, 74.82; H, 7.09; N, 8.44. Found: C, 74.44; H, 7.23; N, 8.30.

EXAMPLE 48

3-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-
4-methoxyphenyl]methoxy]phenyl]-
2-methyl-3H-imidazo[4,5-b]pyridine

Reaction of 2-methyl-3-(4-hydroxyphenyl)-4-azabenzimidazole with (\pm)-3-exo-norbornyloxy-4-methoxybenzyl alcohol, analogous to the procedure of Example 47, yielded the title compound. M.P.: 72-75°C. Elemental Analysis Calc'd for $C_{28}H_{29}N_3O_3$: Calc'd: C, 73.82; H, 6.42; N, 9.22. Found: C, 73.12; H, 6.34; N, 8.86.

-53-

EXAMPLE 49

1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxy-phenyl]methoxy]phenyl-2-butyl-1H-benzimidazole

Diethylazodicarboxylate (90 μ l, 0.580 mmol, 1.2 eq) was added to a mixture of (120 mg, 0.483 mmol, 1.0 eq) 2-butyl-3-(4-hydroxyphenyl)benzimidazole, (126 mg, 0.507 mmol, 1.05 eq) (\pm)-3-*exo*-norbornyloxy-4-methoxybenzyl alcohol, and (139 mg, 0.531 mmol, 1.1 eq) triphenylphosphine in 10 ml anhydrous tetrahydrofuran. After 18 hours at room temperature, the reaction mixture was diluted with 200 ml of ethyl acetate, washed twice with 1N NaOH, once with H₂O, once with brine, dried over MgSO₄, concentrated in vacuo to give 0.2 g of an oil. Silica gel chromatography eluting with 40% ethyl acetate/hexane followed by recrystallization from ether/hexane gave 66 mg, 28%, white crystals. M.P.: 134-136°C. Elemental Analysis Calc'd for C₃₂H₃₆N₂O₃: Calc'd: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.08; H, 6.94; N, 5.43.

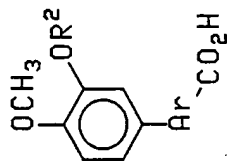
EXAMPLE 50

4-[4-Methoxy-3-(4-phenylbutyloxy)phenyl]benzoic Acid

To a solution of (2.9 g, 8.65 mmol, 1.0 eq) 1-methoxy-2-(4-phenyl-1-butoxy)-4-bromobenzene in 30 ml of dry THF at -78°C was added (3.81 ml, 9.52 mmol, 1.1 eq) 2.5M n-BuLi. After stirring 15 minutes at -78°C, (10.4 ml, 10.4 mmol, 1.2 eq) 1.0M ZnCl₂ in ether was added and the mixture allowed to warm to room temperature over 35 minutes. Tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.43 mmol, 0.05 eq) and (2.27 g, 8.65 mmol, 1.0 eq) methyl-4-iodobenzoate were added to the reaction and the mixture allowed to stir at room temperature for 2.5 hours. The reaction mixture was concentrated in vacuo, costripped with CHCl₃, and chromatographed on a silica gel column eluting with ethyl acetate-hexane (0-10%) to afford 2.61 g, 76%, of a yellow solid. Hydrolysis of the ester according to the method of Example 4 gave the title compound, M.P.: 178-179°C. Elemental analysis calculated for C₂₄H₂₄O₄: C, 76.56; H, 6.43. Found: C, 76.06; H, 5.92.

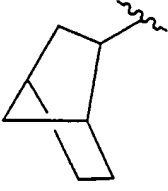
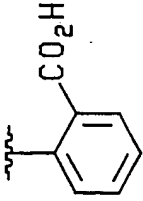
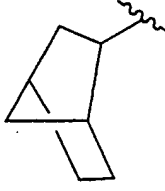
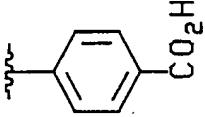
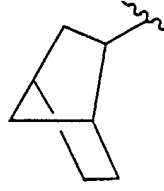
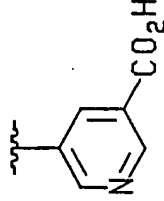
EXAMPLES 51-72

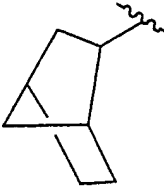
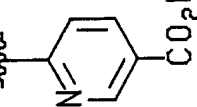

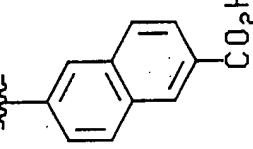

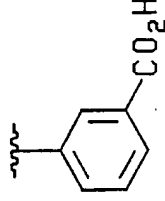
Reaction of the appropriate bromocatechol, with the required halo aromatic ester of the formula X-Ar-C(=O)-OR^1 analogous to the procedure of Example 50, followed by hydrolysis substantially according to the procedure of Example 4 yielded the following compounds of the general formula:


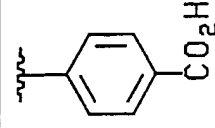
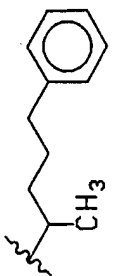
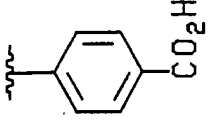

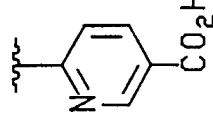


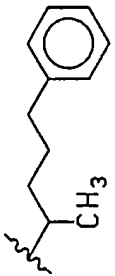
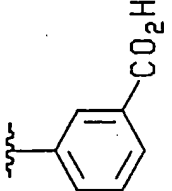
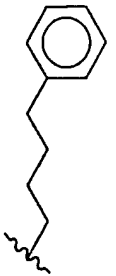
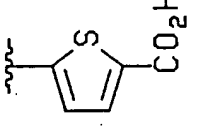
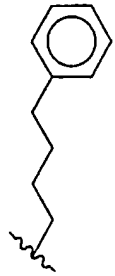
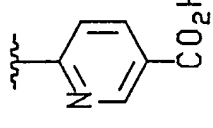
Ex.#	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
51			128-9°	74.54	6.55	--	74.86	6.82	--

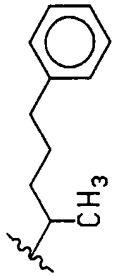
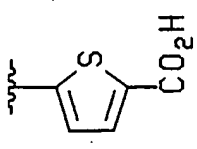
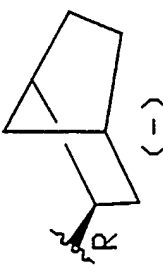
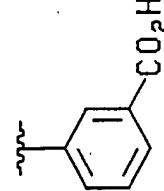
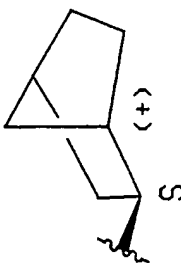
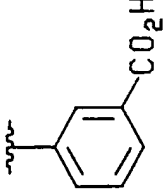
-55-

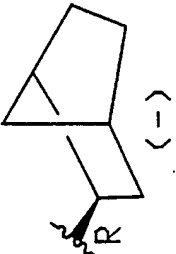
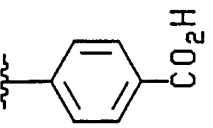
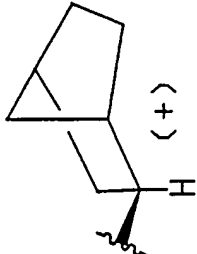
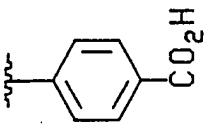
Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
52			66-8°	74.54	6.55	--	75.10	6.20	--
53			230-2°	74.54	6.55	--	74.36	6.20	--
54			236-8°	70.78	6.24	4.13	69.95	6.09	4.17

Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
55			221-3°	70.78	6.24	4.13	70.60	6.08	4.02
56			242-5°	77.30	6.23	--	76.04	5.91	--
57			149-51°	73.05	6.47	--	72.91	6.56	--

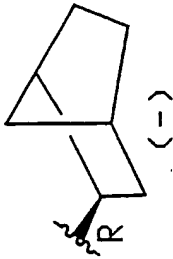
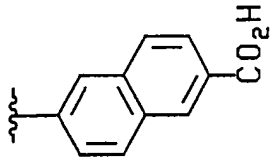
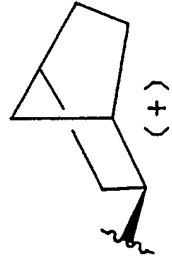
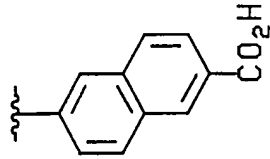
Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
58			230-32°	73.05	6.47	--	73.16	6.51	--
59			136-8°	76.90	6.71	--	76.95	6.48	--
60			148-50°	73.63	6.45	3.58	73.45	6.39	3.65

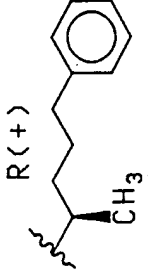
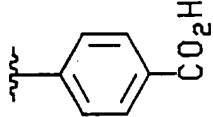
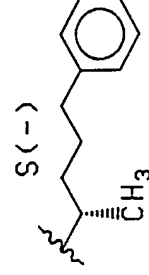
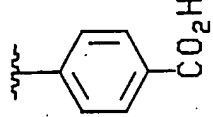
Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
61			72-4°	76.90	6.71	--	77.08	6.49	--
62			118-9°	69.07	5.81	--	68.75	5.61	--
63			188-9°	73.18	6.15	3.71	72.93	6.11	3.69

Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
64			122-4°	--	--	--	--	--	--
65			oil	--	--	--	--	--	--
66			oil	--	--	--	--	--	--

Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
67			234-6°	74.53	6.55	--	74.49	6.24	--
68			234-6°	74.53	6.55	--	74.53	6.17	--

-61-

Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
69			242-4°	77.30	6.23	--	77.28	6.25	--
70			243-5°	--	--	--	--	--	--

Ex. #	R ²	ArCO ₂ H	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
71			159-60°	76.90	6.71	--	76.82	6.58	--
72			159-60°	76.90	6.71	--	76.87	6.69	--

-63-

EXAMPLE 73

2-[(4-Methoxy-4'-nitro[1,1'-biphenyl]-3-yl)oxy]bicyclo[2.2.1]heptane

To a stirred solution of (2 g, 6.73 mmol, 1.0 eq) (\pm)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene in 50 ml of dry THF at -78°C was added 2.96 ml (7.40 mmol, 1.1 eq) 2.5M n-BuLi. After about 45 minutes at -78°C, (8.07 ml, 8.07 mmol, 1.2 eq) 1.0M ZnCl₂ in ether was added and the reaction mixture allowed to warm to room temperature over 30 minutes. Pd (PPh₃)₄ (389 mg, 0.34 mmol, 0.05 eq) and then (1.67 g, 6.73 mmol, 1.0 eq) 1-nitro-4-iodobenzene were added and the reaction mixture stirred 30 minutes at room temperature. The mixture was concentrated in vacuo and chromatographed on silica gel, eluting with ethyl acetate/hexane (0-8%) to afford 1.32 g, 58%, of a yellow solid. M.P.: 134-135°C.

EXAMPLE 74

4'-Methoxy-3'-(1-methyl-4-phenyl-butoxy)-[1,1'-biphenyl]-4-tetrazole

A solution of (525 mg, 8.07 mmol, 1.2 eq) NaN₃ in 10 ml H₂O was added to a stirred solution of (1.8 ml, 6.70 mmol, 1.0 eq) of Bu₃SnCl in 75 ml of ether. The mixture was stirred 45 minutes at room temperature then the layers were separated and the aqueous layer extracted once with ether. The ether extracts were combined, washed once with brine, dried over MgSO₄, and concentrated to yield a clear, colorless oil, used directly in the next reaction.

To a mixture of (2.22 g, 6.7 mmol, 1.7 eq) crude Bu₃SnN₃ in 50 ml dry THF was added a solution (1.5 g, 4.04 mmol, 1.0 eq) of the nitrile (see Preparation 39) in 50 ml dry THF. The reaction mixture was heated to reflux and stirred for 4 days. The mixture was cooled, concentrated in vacuo, and chromatographed on silica gel eluting with hexane-ethyl acetate-acetic acid (75:24:1), then recrystallized from ethyl acetate-hexane to afford 565 mg, 34%, of an off white solid. M.P.: 139-140°C.

EXAMPLE 75

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenoxy] benzoic acid

To a solution (1 g, 4.27 mmol, 1.0 eq) of 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy phenol and (0.63 ml, 4.27 mmol, 1.0 eq) ethyl-4-fluorobenzoate in 45 ml of dimethylacetamide was added (708 mg, 5.12 mmol, 1.2 eq) K₂CO₃. After heating to reflux for 18 hours, the reaction mixture was cooled to room temperature, poured into 75 ml of H₂O and extracted twice with ethyl acetate. The ethyl acetate extracts were

-64-

combined, washed once with brine, dried over MgSO_4 , and concentrated to give a dark brown oil. Chromatography on silica gel eluting with ethyl acetate-hexane (0-15%) gave 590 mg, 26%, of a light yellow oil.

A mixture of (750 mg, 1.96 mmol, 1.0 eq) of the above ester and 10 ml of 2N NaOH in 20 ml of ethanol was heated to reflux for 2 hours. The mixture was diluted with 50 ml of H_2O , acidified to pH 4 and extracted twice with ethyl acetate. The combined organic layers were washed once with brine, dried over Na_2SO_4 , and concentrated to give an off-white solid. Recrystallization from ethyl acetate/hexane afforded 425 mg, 61%, of a white crystalline solid. M.P.: 116-117°C. Elemental Analysis Calc'd for $\text{C}_{21}\text{H}_{22}\text{O}_5$: Calc'd: C, 71.16; H, 6.27. Found: C, 70.98; H, 6.18.

EXAMPLE 76

N-[3'-(Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluoromethanesulfonamide
and

N,N-[3'-(Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy-[1,1'-biphenyl]-4-yl]-bis(1,1,1-trifluorodimethanesulfonamide)

To a mixture of (450 mg, 1.45 mmol, 1.0 eq) of 3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-amino and (0.24 ml, 1.74 mmol, 1.2 eq) triethylamine in 6 ml of CH_2Cl_2 at -78°C was added 0.27 ml (1.60 mmol, 1.0 eq) of triflic anhydride dropwise. The reaction mixture was stirred 10 minutes at -78°C and then 1.5 hours at 0°C. The mixture was concentrated in vacuo, costripped twice with CHCl_3 , then chromatographed on silica gel eluting with ethyl acetate-hexane (10% → 30%) to afford 187 mg, 22%, of N,N-[3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluorodimethanesulfonamide and 70 mg, 11%, of N-[3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluoromethanesulfonamide. M.P. of the dimethanesulfonamide: 146-147°C. M.P. of the methanesulfonamide: 138-139°C. Dimethanesulfonamide Elemental Analysis Calc'd for $\text{C}_{22}\text{H}_{21}\text{NO}_6\text{S}_2\text{F}_6$: Calc'd: C, 46.07; H, 3.70; N, 2.44. Found: C, 46.21; H, 3.63; N, 2.51.

EXAMPLE 77

N-(3'-Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy-[1,1'-biphenyl]-4-ylmethanesulfonamide

To a stirred solution of (525 mg, 1.70 mmol, 1.0 eq) 3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-amino in 10 ml dry CH_2Cl_2 at 0°C was added 0.28 ml of triethylamine (2.03 mmol, 1.2 eq), followed by 355 mg (2.03 mmol, 1.2 eq) methanesulfonic anhydride. The mixture was stirred at 0°C for 10 minutes, then at

-65-

room temperature for 1 hour, at which point an additional 200 mg (1.1 mmol, 0.7 eq) of methane sulfonic anhydride was added. After stirring an additional 30 minutes at room temperature, the reaction mixture was concentrated in vacuo, costripped twice with CHCl_3 , and chromatographed on silica gel eluting with ethyl acetate-hexane (10-35%) to yield 700 mg of compound. Recrystallization from ethyl acetate/hexane afforded 650 mg, 98%, of crystals. M.P.: 151-153°C. Elemental Analysis Calc'd for $\text{C}_{21}\text{H}_{25}\text{NO}_4\text{S}$: Calc'd: C, 65.08; H, 6.51; N, 3.61. Found: C, 64.92; H, 6.21; N, 3.53.

EXAMPLE 78

Methyl 1-[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxyphenyl]-1H-indole-3-carboxylate

A mixture of (1.0 g, 5.71 mmol, 1.0 eq) 3-carbomethoxy indole, (2.21 g, 7.42 mmol, 1.3 eq) (\pm)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene (30.7 mg, 0.107 mmol, 0.2 eq) cuprous bromide, and (866 mg, 6.27 mmol, 1.1 eq) potassium carbonate in 15 ml of 1-methyl-2-pyrrolidinone was heated to 150°C for 24 hours. The reaction mixture was cooled, diluted with 350 ml of ethyl acetate and 350 ml of H_2O , and the layers separated. The aqueous layer was extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H_2O , once with brine, dried over Na_2SO_4 and concentrated in vacuo to give a light brown oil. Silica gel chromatography eluting with 20% ethyl acetate/hexane gave 1.05 g, 47%, of a white foamy solid. M.P.: 120-122°C. Elemental Analysis Calc'd for $\text{C}_{24}\text{H}_{25}\text{NO}_4$: Calc'd: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.70; H, 6.37; N, 3.59.

EXAMPLE 79

1-[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxy]-1H-indole-3-carboxylic acid

A mixture of (0.85 g, 2.17 mmol, 1.0 eq) of methyl 1-[3-(bicyclo[2.2.1]-hept-2-yloxy)-4-methoxyphenyl]-1H-indole-3-carboxylic acid and 20 ml of 1N NaOH in 50 ml of CH_3OH was heated to reflux for 18 hours. The reaction mixture was cooled, diluted with 150 ml of H_2O , and acidified to pH 1. The white precipitate that formed was filtered, washed with H_2O and air dried to yield 0.68 g of a white solid. Recrystallization from ethyl acetate/hexane afforded 565 mg, 69%, of white powder. M.P.: 203-205°C. Elemental Analysis Calc'd for $\text{C}_{23}\text{H}_{23}\text{NO}_4$: Calc'd: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.01; H, 6.23; N, 3.66.

-66-

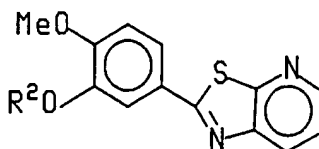
EXAMPLE 80

2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-fluorobenzothiazole

A mixture of (440 mg, 2 mmoles) 4-methoxy-3-cyclopentyloxy benzaldehyde and (400 mg, 2.1 mmoles) 2-mercapto-5-fluoroaniline hydrochloride was heated on a steam bath for 15 minutes. The resulting thick orange oil was cooled and dissolved in 5 ml of 10% FeCl₃ in methanol and allowed to stir overnight. The reaction was diluted with water and extracted with CH₂Cl₂. The CH₂Cl₂ layer was dried and evaporated to give 760 mg of crude product which was purified on silica gel with CH₂Cl₂ to give 500 mg of product. Recrystallization from isopropanol gave 140 mg of product. M.P.: 96-97°C. Elemental Analysis Calc'd for C₁₉H₁₈O₂NSF: Calc'd: C, 66.45; H, 5.28; N, 4.08. Found: C, 66.44; H, 5.13; N, 4.06.

EXAMPLES 81-82

Reaction of the appropriate aldehyde with 2-mercapto-3-aminopyridine, analogous to the procedure of Example 80, yielded the following compounds of the formula



Ex.#	R ²	M.P. °C	Analysis					
			Calculated %			Found %		
			C	H	N	C	H	N
81		118-120°	66.23	5.56	8.58	66.41	5.71	8.42
82		110-111°	--	--	--	--	--	--

-67-

EXAMPLE 83

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
1H-benzimidazole-5-carboxylic acid

A mixture of (800 mg, 5.3 mmoles) cyclopentyl bromide, (1.6 g, 5.3 mmoles) methyl 1-(3-hydroxy-4-methoxyphenyl)-1H-benzimidazole-5-carboxylate and 251 mg of 60% sodium hydride in 10 ml of dimethylformamide was stirred at 100° for 30 minutes. The reaction was cooled, poured onto H₂O and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 2 g of crude product. Purification on silica gel with CH₂Cl₂ gave 1.1 g of methyl 1-(3-cyclopentyl-4-methoxyphenyl)-1H-benzimidazole-5-carboxylate. M.P.: 129-131°.

A solution of 500 mg of the above methyl ester in 20 ml of methanol containing 5 ml of 1N NaOH was heated on a steam bath for 30 minutes. The reaction was cooled and the methanol removed in vacuo. The residue was acidified with 1N HCl and the resulting solid was filtered and recrystallized from methanol to give 198 mg of product. M.P. >250°C.

EXAMPLE 84

2-[3-(Cyclopentyloxy)-4-methoxy-
phenyl]oxazolo[4,5-b]pyridine

A solution of 500 mg of 2-N[3-(cyclopentyloxy)-4-methoxyphenylcarbonyl]amino-3-hydroxypyridine in 15 ml of POCl₃ was heated at reflux for 20 hours. Excess POCl₃ was evaporated and the crude product was purified by chromatography on silica gel with CH₂Cl₂/methanol to give 165 mg of the title product. M.P.: 108-109°C.

EXAMPLE 85

2-[3-(Cyclopentyloxy)-4-methoxy-
phenyl]oxazolo[5,4b]pyridine

Reaction of 4-methoxy-3-cyclopentyloxybenzoic acid chloride with 2-hydroxy-3-amino pyridine, analogous to the procedure of Example 84 yielded the title compound. M.P.: 141-142°C. Elemental Analysis Calc'd for C₁₈H₁₈N₂O₃: Calc'd: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.51; H, 5.76; N, 8.90.

EXAMPLE 86

2-(3-Cyclopentyloxy-4-methoxyphenyl)thiazole

A solution of 130 mg of 3-cyclopentyloxy-4-methoxybenzthioamide and 100 mg of chloroacetaldehyde in 15 ml of ethanol was heated at reflux for 6 hours. The volatiles were evaporated and the residue purified on silica gel with CH₂Cl₂ to give 90 mg of product. M.P.: 72-75°C.

-68-

EXAMPLE 87

2-(3-Cyclopentyloxy-4-methoxy
phenyl)-5-thiazolecarboxylic acid

Reaction of 3-methoxy-4-cyclopentyloxybenzthioamide with chlorocarboethoxy-acetaldehyde, analogous to the procedure of Example 86, yielded the ethyl ester of the title compound, which was hydrolyzed under basic conditions to yield the title compound. M.P.: 170-171°C.

EXAMPLE 88

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxyphenyl]-2-thiazolacetic acid

A solution of (660 mg, 6.5 mmoles) of 4-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-methylthiazole in THF was added dropwise to a solution of lithium diisopropylamide in THF at -78°C. After 1 hour at -78°C dry CO₂ was bubbled into the reaction for 2 minutes. The reaction was allowed to warm to room temperature, acidified with dilute HCl and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 420 mg product. Recrystallization from hexane 290 mg product. M.P.: 190-191°C.

EXAMPLE 89

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-
methoxyphenyl]-2-thiazolecarboxylic acid

Reaction of the chloroketone of Preparation 43 with ethyl thiioxanate, analogous to the procedure of Example 88, yielded the ethyl ester of the title compound which was then hydrolyzed according to the procedure of Example 8 to give the title compound. M.P.: 112-113°C.

EXAMPLE 90

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-
methoxyphenyl]-2-thiazolamine

Reactions of the chloroketone of Preparation 43 with thiourea, analogous to the procedure of Example 88, yielded the title compound. M.P.: 168-178°C.

EXAMPLE 91

1-[3-(Cyclopentyloxy)-4-methoxy-
phenyl]-1H-imidazo[4,5-c]pyridine

A solution of 2.05 g of 1-(3-hydroxy-4-methoxyphenyl)-1H-imidazo[4,5-c]pyridine, 2.5 g of cyclopentylbromide and 665 mg of NaH in 20 ml of DMF was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl

-69-

acetate, dried to give 1.4 g of crude product. Recrystallization from CH_2Cl_2 gave 574 mg product. M.P.: 66-68°C.

EXAMPLE 92

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
2-methyl-1H-imidazo[4,5-c]pyridine

Reaction of 3-hydroxy-4-methoxy-N-[4-(3-amino)pyridinyl]aniline with acetic acid, analogous to the procedure of Preparation 44, and subsequent reactions with cyclopentylbromide analogous to the procedure of Example 91, yielded the title compound. M.P.: 144-145°C.

EXAMPLE 93

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
2-ethyl-1H-imidazo[4,5-c]pyridine

Reaction of 3-hydroxy-4-methoxy-N-[4-(3-amino)pyridinyl]aniline with propionic acid analogous to the procedure of Preparation 44, and subsequent reaction with cyclopentylbromide, analogous to the procedure of Example 91, yielded the title compound.

EXAMPLE 94

2-[3-[2-Indoxy]-4-methoxyphenyl]-1H-imidazo[4,5-b]pyridine

A. Preparation of 3-(2-indoxy)-4-methoxybenzoic acid

To a magnetically stirred solution of 3-(2-indoxy)-4-methoxybenzaldehyde (3.0 g, 11.2 mmoles) in acetone (50 ml) was added 7 ml of 2.67 M solution of Cr_2O_3 in 50% aqueous H_2SO_4 . This was exothermic enough to effect a mild reflux of acetone, and no external cooling was necessary. After stirring overnight at ambient temperature, 50 ml of H_2O was added, and the acetone was allowed to evaporate over a steam bath. The crude product was filtered and washed with 1N HCl followed by water. Recrystallization from isopropyl ether gave 1.9 g of off-white crystals. M.P.: 189-191°C.

B. Preparation of 3-(2-indoxy)-4-methoxybenzoyl chloride

A solution of 0.50 g of 3-(2-indoxy)-4-methoxybenzoic acid in 10 ml of thionyl chloride was heated at reflux for 1 hour. Removal of the volatiles under reduced pressure gave a dull pink solid which was immediately used in the next step without purification.

-70-

C. Preparation of the title compound

To a magnetically stirred solution of 2,3-diaminopyridine (1.8 mmole) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxybenzoyl chloride in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.59 g of a white solid. M.P.: 226-228°C (dec).

The above amide was suspended in 10 ml of phosphorous oxychloride and heated at reflux for 1.5 hours, at which time the reaction mixture was homogeneous. The volatiles were removed under reduced pressure, and the residue was suspended in 25 ml of saturated sodium bicarbonate, filtered, and air-dried. Column chromatography followed by recrystallization from ethanol gave 180 mg of off-white crystals. M.P.: 206-208°C. Elemental analysis calculated for $C_{22}H_{19}O_2N_3$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.01; H, 5.06; N, 11.76.

EXAMPLE 95

2-[3-[2-Indoxy]-4-methoxyphenyl]thiazo[5,4-b]pyridine

A. Preparation of 3-amino-2-thiopyridine

A mixture of 3-amino-2-chloropyridine (25 g, 190 mmoles), sodium hydrogen sulfide (58 g, 780 mmoles) and propylene glycol (75 ml) were heated at reflux for 5 hours. The solvent was removed under reduced pressure, and the resulting residue was dissolved in 300 ml of water and acidified to pH 5 with AcOH. After stirring for 1 hour the mixture was filtered to give 14.3 g of a dark brown solid. Recrystallization from toluene provided dark brown needles. M.P.: 131-132°C.

B. Preparation of the title compound

To a magnetically stirred solution of 3-amino-2-thiopyridine (0.22 g) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxybenzoyl chloride (0.50 g) in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.60 g of a gold solid. M.P.: 252-253°C (dec).

The above amide (0.58 g, 1.5 mmoles) and $POCl_3$ (10 ml) were heated at reflux. After 1.5 hours the mixture was slowly poured into water, cooled, and extracted with ether. The combined organics were dried over $MgSO_4$ and concentrated to give a pale yellow solid. Recrystallization from methanol gave 0.32 g of product as its HCl salt.

-71-

The salt was dissolved in methylene chloride and washed with 1N NaOH to give a white solid. Recrystallization from methanol gave 0.25 g of a white solid. M.P.: 159-160°C. Elemental analysis calculated for $C_{22}H_{18}O_2N_2S$: C, 70.57; H, 4.84; N, 7.48. Found: C, 70.46; H, 4.72; N, 7.35.

EXAMPLE 96

2-[3-[2-Indoxy]-4-methoxyphenyl]oxazo[5,4-b]pyridine

A. Preparation of 3-amino-2-pyridone

3-Nitro-2-pyridone (2.0 g, 14 mmol), 10% Pd/C (0.20 g) and methanol (50 ml) were placed on a Parr shaker under 45 psi of H_2 . After 18 hours the mixture was filtered and concentrated to give 1.3 g of a pale pink solid. M.P.: 123-125°C.

B. Preparation of the title compound

To a magnetically stirred solution of 3-amino-2-hydroxypyridine (1.8 mmol) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxybenzoyl chloride in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.57 g of a white solid. M.P.: 282-284°C (dec).

The above amide was suspended in 10 ml of phosphorous oxychloride and heated at reflux for 1.5 hours, at which time the reaction mixture was homogeneous. The volatiles were removed under reduced pressure, and the residue was suspended in 25 ml of saturated sodium bicarbonate, filtered, and air-dried. Column chromatography (silica, 1:3 EtOAc/hexane) gave 160 mg of a white solid. M.P.: 193-194°C.

EXAMPLE 97

4'-Methoxy-3'-(4-phenylbutoxy)- (±)[1,1'-biphenyl]-4-carboxamide

A suspension of (0.522 g, 1.38 mmol) 4-[4-methoxy-3-(4-phenylbutoxy)phenyl]benzoic acid in dry methylene chloride was treated with excess thionyl chloride (0.505 ml, 6.93 mmol) and a catalytic amount of anhydrous DMF (3-5 drops). The resulting clear solution was heated to reflux under nitrogen atmosphere for 1 hour. The methylene chloride was removed in vacuo and the resulting light yellow solid residue azeotroped with additional 15 ml of dry methylene chloride. The residue was dissolved in 15 ml of dry CH_2Cl_2 , cooled to 0°C (ice bath) and dry anhydrous ammonia gas bubbled directly into the reaction mixture for approximately 5 minutes. This was

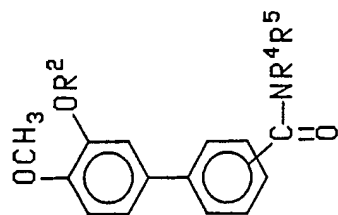
-72-

followed by allowing the reaction to stir at 0°C for an additional hour, after which time the reaction mixture was diluted with 500 ml of ethyl acetate and 300 ml of H₂O. The organic layer was separated and washed with 1N HCl (2 x 350 ml), 2N NaOH (2 x 350 ml), water (1 x 300 ml), brine, dried over MgSO₄ and evaporated under reduced pressure which yielded a white solid. Recrystallization from ethyl acetate-hexane gave a total of 0.37 grams of white crystals. M.P.: 180-182°C. Elemental Analysis Calc'd for C₂₄H₂₅O₃N: Calc'd: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.93; H, 6.71; N, 3.73.


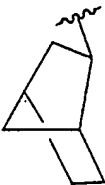
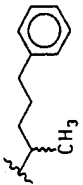


-73-

EXAMPLES 98-104

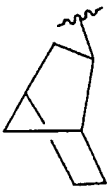
Reaction of the appropriate carboxylic acid with the required amine of the general formula NR_1R_2 , analogous to the procedure of Example 97, yielded the following compounds:



Ex.#	R ²	R ⁴	R ⁵	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
98		H	H	Para	183-184°	--	--	--	--	--	--

Ex.#	R ²	R ⁴	R ⁵	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
99		H	H	Para	N.T.	77.09	6.49	3.60	76.75	6.67	3.55
100		CH ₂ CH ₃	CH ₂ CH ₃	Meta	112-114°	76.30	7.94	3.56	76.55	8.22	3.61
101		H	H	Para	169-171°	77.08	7.08	3.59	77.07	6.95	3.59
102		H	CH ₃	Para	98-100°	77.39	7.24	3.47	77.31	7.24	3.45
103		H	H	Meta	151-153°	74.75	6.87	4.15	74.47	6.97	4.00

-75-

Ex. #	R ²	R ⁴	R ⁵	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
104		H	H	Para	245-247°	--	--	--	--	--	--

-76-

EXAMPLE 105

N-(2-Methylphenyl)sulphonyl
4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-
(+)[1,1'-biphenyl]-4-carboxamide,

To a solution of acid 4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-(+) [1,1'-biphenyl]-4-carboxylic acid, (0.257 g, 0.658 mmoles) in 10 ml of anhydrous methylene chloride under hydrogen atmosphere was added dimethylamino pyridine (88.46 mg, 0.728 mmoles); o-Toluenesulfonamide (0.122 g, 0.712 mmoles) and dicyclohexylcarbodiimide (0.124 g, 0.6 mmoles) the reaction mixture allowed to stir for 50 hours. The solvent was evaporated and the resulting solid triturated with methylene chloride:ether (~1:1) which lead to precipitation of by-product DCU which was filtered. Concentration of the mother liquor followed by 3 g additional triturations with ethyl acetate/ether (~1:1) caused additional deposit of white solid which was filtered. The clear filtrate was concentrated and purified on a silica gel column using methylene chloride/methanol as eluant (95:5). Concentration of fractions containing desired products gave a total of 0.37 g of white foamy solid. Recrystallization from ethyl acetate/hexane gave 0.208 grams of white solid. M.P.: 97-100°C.

EXAMPLE 106

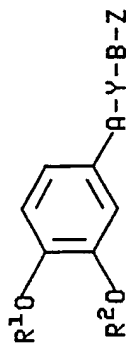
2-[3-[4-(4-Methoxyphenyl)butoxy]-4-methoxy
phenyl]-1H-benzimidazole-5-carboxylic Acid

3-(4-(4-Methoxyphenyl)-butoxy)-4-methoxybenzaldehyde (2.8 g) and 3,4-diaminobenzoic acid (1.4 g) were heated to about 120°C over 1 hour. The resulting residue was chromatographed on a 5 x 10 cm pad of silica gel eluting with ether to give 1.4 g of a beige solid which was recrystallized from 20 ml of methanol. M.P. 167-169°C. MS m/e 450 ($M^+ + 1$). Elemental analysis calculated for $C_{26}H_{28}O_5N_2$: C, 69.62; H, 6.29; N, 6.24. Found: C, 69.72; H, 6.70; N, 5.75.

-77-

EXAMPLES 107-211


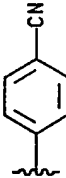

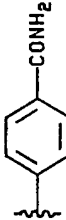
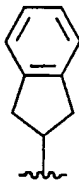
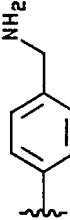

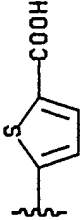

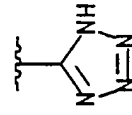
Additional examples which were prepared according to the methods described and readily apparent to those skilled in the art are shown in the following table.


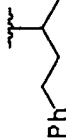
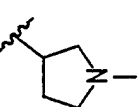
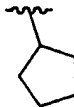



C.B. = Covalent Bond

Ex. #	R ¹	R ²	A	Y	B	Z-R ³	M.P.(°C)
107	CH ₃		C.B.	C.B.	C.B.		244-247
108	CH ₃		C.B.	C.B.	C.B.		119-122 dec.
109	CH ₃		C.B.	C.B.	C.B.		118-119
110	CH ₃		C.B.	C.B.	C.B.		188-189

-78-

Ex. #	R ¹	R ²	A	Y	B	Z-R ³	M.P. (°C)
111	CH ₃		C.B.	C.B.	C.B.		199-201
112	CH ₃		C.B.	C.B.	C.B.		237-239
113	CH ₃		C.B.	C.B.	C.B.		128-129
114	CH ₃		C.B.	C.B.	C.B.		122-124
115	CH ₃		C.B.	C.B.	C.B.		139-140

Prep.#	R'	R	R ²	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
4	CH ₃	3-NO ₂		63.5°	237.3	--	60.75	6.37	60.58	6.05
5	CH ₃	4-CHO	 (±)	oil	284.4	284	--	--	--	--
6	CH ₃	4-CHO	 (±)	oil	235.3	235	--	--	--	--
7	C ₂ H ₅	3-CHO		oil	234.3	234	71.76	7.74	71.74	8.00
8	C ₂ H ₅	3-CHO	 sm = endo prod = exo	oil	260.2	260	--	--	--	--

-120-

PREPARATION 9

Bis(2-methoxy-5-bromophenyl)carbonate

Dissolved (8.26 ml, 160 mmol, 2.2 eq) bromine in 10 ml of CHCl_3 and then added it dropwise over 10 minutes to (20.0 g, 72.9 mmol, 1.0 eq) of bis(2-methoxyphenyl)carbonate in 60 ml of CHCl_3 at room temperature. Stirred for 60 minutes at room temperature, then filtered the reaction mixture, washing the precipitate three times with CHCl_3 and once with hexane. The precipitate was recrystallized from CHCl_3 to yield 20.7 g, 66% yield, of bis(2-methoxy-5-bromophenyl)carbonate as white prisms.

PREPARATION 10

5-Bromoguaiacol

A suspension of (20.7 g, 47.9 mmol, 1.0 eq) bis(2-methoxy-5-bromophenyl)carbonate in 250 ml methanol and 60 ml (120 mmol, 2.5 eq) of 2N NaOH was refluxed for 2 hours. The reaction mixture was cooled to room temperature, concentrated to a volume of ca 100 ml, and poured into 1 L of H_2O . The pH was adjusted to 2 using 1N HCl. The acidic mixture was transferred to a separatory funnel, and extracted three times with ether. The ether extracts were combined and washed once with H_2O , once with brine, and then dried over anhydrous sodium sulfate. Filtration, concentration and drying afforded 19.0 g of a white solid, which was recrystallized from petroleum ether to yield 17.63 g, 91% yield, of white prisms.

PREPARATION 11

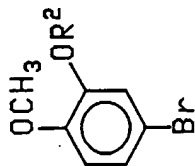
2-(5-Bromo-2-methoxyphenoxy)bicyclo[2.2.1]heptane

Neat diethylazodicarboxylate (1.4 ml, 8.87 mmol, 1.2 eq) was added to a 25°C solution of (1.50 g, 7.39 mmol, 1.0 eq) 5-bromoguaiacol, (2.13 g, 8.13 mmol, 1.1 eq) triphenylphosphine and (0.829 g, 7.39 mmol, 1.0 eq) of S(-)-endo-norborneol in 25 ml of anhydrous tetrahydrofuran. After stirring 18 hours at room temperature under N_2 , the reaction mixture was diluted with 350 ml of ether, washed twice with 1N NaOH, once with H_2O , once with brine, and then dried over anhydrous Na_2SO_4 . Filtration, concentration and drying afforded a yellow oil which was triturated with ca 250 ml of 1:1 ether-hexane to remove triphenylphosphine oxide. The filtrate was concentrated in vacuo, and chromatographed on a silica gel column, eluting with 10% ethyl acetate-hexane, to afford 1.75 g, 80% yield, of a clear, colorless oil. Elemental Analysis: Calc'd for $\text{C}_{14}\text{H}_{17}\text{O}_2\text{Br}$: Calc'd: C, 56.57; H, 5.77%. Found: C, 56.68; H, 5.73%.

-121-


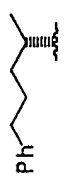
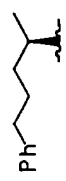
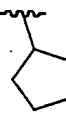
PREPARATIONS 12-18

Reaction of 5-bromoguaiacol with the requisite alcohol with the formula R^2-OH , analogous to the procedure of Preparation 11, afforded the following compounds:




Prep.#	R ²	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
12	 endo = sm exo = prod	oil	297.3	298	--	--	--	--
13	 Ph	oil	349.3	350	--	--	--	--

-122-

Prep.#	R ²	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
14	 R(+) = sm S(+) = prod	oil	297.2	298	56.57	5.77	56.74	5.72
15	 R(-) = sm S(+) = prod	oil	349.29	349.2	61.89	6.09	61.18	6.10
16	 S(+) = sm R(+) = prod	oil	349.29	349.2	61.89	6.09	59.77	5.66
17		oil	271.17	271.1	53.16	5.58	53.41	5.62

-123-

Prep.#	R ²	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
18		oil	335.26	--	--	--	--	--

sm = starting material
prod = product

-124-

PREPARATION 19

4-(Difluoromethoxy)-3-hydroxybenzaldehyde

Dissolved (5.00 g, 36.2 mmol, 1.0 eq) of 3,4-dihydroxybenzaldehyde in 60 ml of 1,4-dioxane, then added 24 ml of H₂O and 36.2 ml (72.4 mmol, 2.0 eq) of 2N NaOH to the above solution at room temperature. After heating to 70°C external, chlorodifluoromethane was bubbled into the reaction mixture for 50 minutes, maintaining a temperature of 60-70°C. The reaction mixture was cooled to room temperature, concentrated in vacuo, diluted with 1 L H₂O and the pH adjusted to 5 using 1N HCl. The aqueous layer was then transferred to a separatory funnel, extracted four times with 300 ml each of ethyl acetate. The ethyl acetate layers were combined and washed once with brine and dried over anhydrous Na₂SO₄. The crude product was chromatographed over silica gel eluting with 25% ethyl acetate-hexane. Yield was 1.30 g, 19%, as a white solid. Elemental Analysis: Calc'd for C₈H₆O₃F₂: Calc'd: C, 51.08; H, 3.22. Found: C, 51.10; H, 3.14. NMR (300 MHz, CDCl₃): δ 6.65 (1H, t), δ 9.91 (1H, s). M.P.: 82-83°C.

PREPARATION 20

3-(Difluoromethoxy)-4-hydroxybenzaldehyde

The title compound is prepared according to the reaction procedure of Preparation 19. The title product was isolated from the reaction mixture by column chromatography. M.P.: 64-66°C. NMR (300 MHz, CDCl₃): δ 6.61 (1H, t), δ 9.83 (1H, s).

PREPARATION 21

3-Bicyclo[2.2.1]hept-2-yloxy-4-difluoromethoxybenzaldehyde

Into a stirred solution of (3.28 g, 14.1 mmol, 1.0 eq) of (\pm)-3-exo-norbornyloxy-4-hydroxybenzaldehyde in 200 ml of 2N NaOH and 100 ml of dioxane at 70°C was bubbled in HCF₂Cl gas. The reaction mixture was poured into 400 ml of H₂O, acidified, and extracted with ether twice. The ether extracts were combined, washed twice with saturated NaHCO₃ solution, once with H₂O, once with brine, and dried over MgSO₄, then concentrated to yield 4 g of crude product. Flash chromatography on silica gel eluting with 15% ethyl acetate-hexane yielded 1.3 g, 33%, of an oil. Mass Spectra (M⁺): 282. NMR (300 MHz, CDCl₃): δ 9.90 (s, 1H), δ 6.64 (t, 1H).

-125-

PREPARATION 22

3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-hydroxybenzaldehyde

A mixture of (500 mg, 2.03 mmol, 1.0 eq) (\pm)-3-exo-norbornyloxy-4-methoxybenzaldehyde and (201 mg, 2.87 mmol, 1.4 eq) sodium thiomethoxide in 10 ml of anhydrous DMF was heated at 50-60°C for 20 hours. The reaction mixture was poured into 150 ml 0.5 N HCl and extracted twice with ether. The ether extracts were combined, washed twice with saturated NaHCO₃, once with H₂O, once with brine, dried over MgSO₄, and then concentrated to give 0.5 g of an oil. Flash chromatography on silica gel, eluting with 15% ethyl acetate/hexane, yielded 320 mg, 72%, of an oil.

Mass Spectra (M⁺): 232. NMR (300 MHz, CDCl₃): δ 9.76 (s, 1H).

PREPARATION 23

2-Bicyclo[2.2.1]hept-2-yloxy)-
4-[(methylthio)methyl]phenol

A solution of (9.00 g, 122 mol, 5.0 eq) sodium thiomethoxide, (6.00 g, 24.4 mmol, 1.0 eq) (\pm)-3-exo-norbornyloxy-4-methoxybenzaldehyde in 120 ml of anhydrous dimethylformamide was heated to reflux under N₂ for 45 minutes. The reaction mixture was cooled, poured into 500 ml of 0.5 N HCl, extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed four times with H₂O, once with brine, dried over Na₂SO₄, and then concentrated to yield 6.85 g of a brown oil. Silica gel chromatography eluting with 10% ethyl acetate-hexane afforded 1.47 g, 26%, of a pale yellow oil. Elemental Analysis: Calcd. for C₁₅H₂₀O₂S: Calc'd: C, 68.14; H, 7.62; S, 12.13. Found: C, 68.10; H, 7.28; S, 12.38. M.P. = 75-77°C.

PREPARATION 24

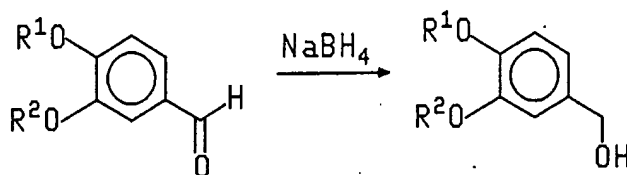
3-(Bicyclo[2.2.1]hept-2-yloxy-4-
methoxy- α -methylbenzenemethanol

Added (108 mg, 2.85 mmol, 1.1 eq) sodium borohydride to a stirred solution of (675 mg, 2.59 mmol, 1.0 eq) (\pm)-3-methoxy-4-exo-norbornyloxy-acetophenone in 15 ml MeOH and 15 ml tetrahydrofuran. After 2 hours at room temperature, the reaction mixture was concentrated, poured into 200 ml of ethyl acetate, washed once with H₂O, once with brine, dried over Na₂SO₄, and then concentrated to yield 0.72 g of a clear oil. Silica gel chromatography eluting with 10% ethyl acetate/CH₂Cl₂ afforded 672 mg, 99%, of a clear oil. Mass spectra (M⁺): 262.

-126-

PREPARATIONS 25-28

Reaction of the following aldehydes, analogous to the procedure of Preparation 24 afforded the corresponding alcohols:



Prep.#	R ²	R ¹	M.W.	Mass Spec. (M ⁺)
25		HF ₂ C	284.3	284
26		H ₃ C	286.4	286
27	H ₃ C		222.2	--
28		H ₃ C	300.4	300

PREPARATION 29

3-Cyclopentyl-4-methoxybenzoic acid

To a stirred suspension of (5.0 g, 27 mmol, 1.0 eq) methyl vanillate, (2.5 ml, 27 mmol, 1.0 eq) cyclopentanol, and (7.4 g, 28 mmol, 1.05 eq) triphenylphosphine in 40 ml of anhydrous tetrahydrofuran was added (4.7 ml, 29.7 mmol, 1.1 eq) of diethylazodicarboxylate. The reaction mixture was stirred 18 hours at room temperature, concentrated in vacuo, and flash chromatographed on a silica gel column, eluting with 20%

-127-

ethyl acetate/hexane, to yield 7.0 g, >100%, of an oil, methyl-3-methoxy-4-cyclopentyl-oxybenzoate.

A mixture of (7.0 g, 27 mmol, 1.0 eq) methyl-3-methoxy-4-cyclopentyl-oxy benzoate, 8 ml (42 mmol, 1.5 eq) 5N NaOH and 40 ml MeOH was refluxed for 3 hours. The mixture was concentrated to ca 20 ml, poured into 400 ml H₂O (pH 10) and washed twice with ether. The aqueous layer was acidified to pH 1 and extracted twice with ether. The ether extracts were combined, washed once with H₂O, once with brine, dried over MgSO₄ and then concentrated to yield 6 g of a white solid. Recrystallization from ether-hexane yielded 5.60 g, 88%, of white crystals. Elemental Analysis: Calcd. for C₁₃H₁₆O₄: Calc'd: C, 66.09; H, 6.83. Found: C, 66.20; H, 6.64.

PREPARATION 30

3-Cyclopentyl-oxy-4-methoxybenzylbromide

To a stirred solution of (4.4 g, 20 mmol, 1.0 eq) 3-cyclopentyl-oxy-4-methoxybenzyl alcohol in 100 ml anhydrous tetrahydrofuran at 0°C was added portionwise (9.2 g, 22 mmol, 1.1 eq) dibromotriphenylphosphorane over 10 minutes. The reaction was stirred at 0°C for 1 hour, then allowed to warm to room temperature over 2 hours. The mixture was poured into 400 ml H₂O and extracted twice with 400 ml ether. The ether extracts were combined, washed once with saturated NaHCO₃, once with H₂O, once with brine, dried over MgSO₄, and then concentrated to give 10 g of a solid. Trituration with 10% ether-hexane followed by concentration of the filtrate gave ca. 2 g of an oil. Flash chromatography on silica gel eluting with 15% ethyl acetate-hexane yielded 2.17 g, 38%, of an oil.

PREPARATION 31

Phosphonium, [3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy]methyl]triphenyl-, bromide

A mixture of (2.1 g, 7.36 mmol, 1.0 eq) 3-cyclopentyl-oxy-4-methoxybenzylbromide and (1.93 g, 7.36 mmol, 1.0 eq) triphenylphosphine in 50 ml of anhydrous toluene was heated to reflux for 18 hours. The resulting suspension was diluted with 50 ml hexane, cooled to 0°C, and filtered. The filtrant was washed with hexane and dried to yield 3.02 g, 73%, of a solid. M.P. = 228-230°C.

-128-

PREPARATION 32

1-(5-Bromo-2-methoxyphenoxy)-1-(3-phenylpropyl)cyclopropane

(a) Preparation of 2-(5-bromo-2-methoxyphenoxy)-5-phenyl-1-pentene

Tebbe reagent (prepared from titanocene dichloride and trimethyl aluminum) (30 ml of a 0.55M solution in toluene) was added dropwise to a solution of (5-bromo-2-methoxyphenyl)-1-phenylbutyrate, pyridine (0.25 ml), anhydrous tetrahydrofuran (10 ml), and anhydrous toluene (30 ml) at about 0°C. The reaction mixture was warmed to room temperature for about 2 hours, re-cooled to about 0°C and quenched with 3N sodium hydroxide (6 ml). After gas evolution had ceased, ether was added and the mixture was dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography through a short column of basic alumina eluted with 25% petroleum ether/ether afforded 4.4 g of a yellow oil. Mass spectra calculated for $C_{18}H_{19}BrO_2$: 347.2. Found: 347.

(b) Preparation of the title compound

The above oil (4.4 g) was dissolved in anhydrous ether (8 ml) and treated with methylene iodide (1.2 ml) followed by zinc-copper couple (0.9 g) and iodine (5 mg). After heating at reflux for about 17 hours the mixture was filtered and the solid washed with ether. The combined organics were washed with saturated aqueous ammonium chloride, saturated aqueous bicarbonate, brine, dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography on silica gel column eluting with ethyl acetate-hexane (0-10%) afforded 3.2 g of a colorless oil. Mass spectra calculated for $C_{19}H_{21}BrO_2$: 361.3. Found: 362.

PREPARATION 33

3'-Bicyclo[2.2.1]hept-2-yloxy-4'-methoxy-1,1'-biphenyl-4-amino

A mixture of (1.7 g, 5.01 mmol, 1.0 eq) of 2-[(4-methoxy-4'-nitro-[1,1'-biphenyl]-3-yl)oxy]bicyclo[2.2.1]heptane and 1.5 g of 10% Pd/C in 100 ml ethyl acetate was shaken on a Parr hydrogenation apparatus under 40 psi H_2 at room temperature for 10 minutes. The reaction mixture was filtered through celite, concentrated in vacuo, and the residue chromatographed on silica gel eluting with $CH_3OH-CH_2Cl_2$ (1% → 2½%) to afford 1.45 g, 95%, of a white waxy solid. M.P.: 46-50°C.

-129-

PREPARATION 343-[3-Bicyclo[2.2.1]hept-2-yloxy)-4-
(difluoromethoxy)phenyl]pentanediamide

A mixture of (3.40 g, 12.0 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxybenzaldehyde, (334 μ l, 3.37 mmol, 0.28 eq) piperidine and (3.06 g, 36.0 mmol, 3.0 eq) cyanoacetic acid in 50 ml of anhydrous pyridine was heated to reflux for 17 hours. The reaction mixture was cooled to room temperature, diluted with H₂O and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed twice with 1N HCl, once with saturated NaHCO₃, once with H₂O, once with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with 1:3 ethyl acetate:hexane to yield 2.13 g, 51%, of a yellow oil. Elemental Analysis: Calc'd for C₁₉H₂₀N₂O₂F₂: Calc'd: C, 65.87; H, 5.82; N, 8.09. Found: C, 65.53; H, 5.63; N, 8.25.

H₂O₂ (250 ml of 30%, 29.2 mmol, 5.0 eq) was added dropwise to a 0°C mixture of (2.02 g, 5.83 mmol, 1.0 eq) 2-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxyphenyl]propane-1,3-dinitrile and 1.67 ml of 10% aqueous Na₂CO₃ in 30 ml of acetone and 15 ml of H₂O. After stirring 1 hour at 0°C, the reaction mixture was allowed to warm to room temperature and was left stirring for 72 hours. The reaction mixture was poured into 550 ml of ethyl acetate and 400 ml of H₂O and stirred for 1 hour. The 2 layers were separated, and the aqueous layer was extracted four times with ethyl acetate. The ethyl acetate extracts were combined, washed once with H₂O, once with brine, dried over Na₂SO₄ and concentrated to yield 2.0 g of a white solid. Silica gel chromatography eluting with 10% CH₃OH-CH₂Cl₂ afforded 1.29 g, 58%, of a white powder. M.P.: 168-169°C. Elemental Analysis: Calc'd for C₁₉H₂₄N₂O₄F₂: Calc'd: C, 59.67; H, 6.33; N, 7.33. Found: C, 59.60; H, 5.99; N, 7.11.

PREPARATION 35Methyl 2-butyl-1-(4-hydroxyphenyl)-
1H-benzimidazole-5-carboxylate

A mixture of (1.5 g, 6.98 mmol, 1.0 eq) methyl-3-nitro-4-chlorobenzoate and (760 mg, 6.98 mmol, 1.0 eq) 4-aminophenol in 30 ml dry dimethylsulfoxide was heated to reflux for 18 hours. The mixture was poured into 300 ml of H₂O, acidified to pH 5 and extracted once with ether. The resulting sludge was filtered through celite, and the filtrate layers separated. The aqueous layer was extracted with ether, and the ether extracts were combined, washed twice with H₂O, once with brine, dried over MgSO₄,

-130-

and concentrated to give 3.0 g of an oil. Silica gel chromatography eluting with 30% ethyl acetate-hexane gave 850 mg, 42%, of a dark red gum.

A mixture of (850 mg, 2.95 mmol, 1.0 eq) of methyl 4-[(4-hydroxyphenyl)amino]-3-nitrobenzoate and 850 mg of 10% Pd/C in 40 ml ethyl acetate was placed on a Parr hydrogenation apparatus and shaken for 3 hours under 40 psi H₂. The mixture was filtered through celite, concentrated, and chromatographed on a silica gel column eluting with 40% ethyl acetate/hexane to yield 470 mg, 56%, of an off-white solid.

A mixture of (436 mg, 1.69 mmol, 1.0 eq) methyl 4-[4-hydroxyphenylamino]-2-aminobenzoate and 3 ml of valeric anhydride was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature and flash chromatographed on a silica gel column eluting with 10% ethyl acetate/CH₂Cl₂ to give an oil, which was taken up in 15 ml MeOH and treated with 5 ml 1N NaOH for 1 hour. The mixture was poured into 300 ml of H₂O, acidified to pH 5 and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 0.6 g of an oil. Flash chromatography on silica gel eluting with 2½% CH₃OH/CH₂Cl₂ gave 345 mg, 63%, of white foam. Mass Spectra: 324.2.

PREPARATION 36

4-3H-Imidazo[4,5-b]-2-butylpyridinephenol

A mixture of (1.0 g, 4.33 mmol, 1.0 eq) 4-[(2-nitro-4-pyridinyl)amino]phenol and 500 mg of 10% Pd/C in 100 ml of tetrahydrofuran and 100 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H₂ for 1 hour. The reaction mixture was filtered through celite and the filtrate concentrated in vacuo to give 1.01 g, >100%, of a tan solid.

A mixture of 900 mg (4.47 mmol, 1.0 eq) of the above diamine in 10 ml of valeric anhydride was heated to reflux for 3 hours. The reaction mixture was poured into 150 ml of 0.5N HCl, stirred 5 minutes, washed once with ether and the ether wash extracted with 0.5N HCl. The acidic extracts were combined, basified to pH 10 and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed once with 0.5N NaOH, once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 5% CH₃OH/CH₂Cl₂ gave 900 mg, 57%, of an oil.

A mixture of (908 mg, 2.47 mmol, 1.0 eq) butyl 4-(2-butyl-1H-imidazo[4,5-c]pyridin-1-yl)benzoate and 6 ml (6 mmol, 5.0 eq) of 1N NaOH in 25 ml methanol was

-131-

stirred at room temperature for 2 hours. The reaction mixture was concentrated to ca. 10 ml, poured into 200 ml of H₂O, and extracted twice with ether. The aqueous layer was neutralized and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 1 g of solid. Silica gel chromatography eluting with 10% CH₃OH/CH₂Cl₂ yielded 590 mg, 89%, of white solid. M.P.: 161-163°C.

PREPARATION 37

4-(2-Methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenol

A mixture of (3.5 g, 22 mmol, 1.0 eq) 2-chloro-3-nitro-pyridine, (3.65 g, 22 mmol, 1.0 eq) KI, (1.85 g, 22 mmol, 1.0 eq) NaHCO₃, and (2.40 g, 22 mmol, 1.0 eq) 4-amino-phenol in 25 ml of dry dimethylformamide was heated to reflux for 18 hours. The mixture was poured into 400 ml of H₂O, neutralized to pH 7 and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with 5% Na₂S₂O₃, once with H₂O, once with brine, dried over MgSO₄ and concentrated to give 4.8 g of a black solid. Flash chromatography on silica gel eluting with 50% ethyl acetate/CH₂Cl₂, followed by crystallization from isopropyl ether/CH₂Cl₂ gave 3.7 g, 73%, of an orange-red solid.

A mixture of (3.6 g, 15.6 mmol, 1.0 eq) the nitropyridine and 0.9 g of 10% Pd/C in 50 ml of tetrahydrofuran and 50 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H₂ for 1 hour. The mixture was filtered through celite, concentrated in vacuo (4 g purple solid), and flash chromatographed on a silica gel column eluting with 10% CH₃OH/CH₂Cl₂ to give 3.5 g of solid. Trituration from ethyl acetate gave 3.0 g, 96%, of a pink solid.

A mixture of (1.0 g, 4.97 mmol, 1.0 eq) 4-[(3-amino-2-pyridinyl)amino]phenol in 25 ml of valeric anhydride was heated to reflux for 8 hours. The reaction mixture was cooled, poured into 150 ml of 0.5N HCl, stirred 10 minutes, and extracted twice with ether. The ether extracts were combined, washed three times with saturated NaHCO₃, once with H₂O, once with brine, dried over MgSO₄, and concentrated to give an oil. The oil was taken up in 100 ml CH₃OH and treated with 60 ml of 2N NaOH and allowed to stir at room temperature for 1 hour. The mixture was concentrated, poured into 200 ml of H₂O and washed twice with ether. The aqueous layer was neutralized, and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed

-132-

once with H₂O, dried over MgSO₄, and concentrated to give 0.7 g of a solid. Silica gel chromatography eluting with 10% CH₃OH/CH₂Cl₂ gave 510 mg, 38%, of a solid. M.P.: 268-269°C.

PREPARATION 38

2-Butyl-3-(4-hydroxyphenyl)benzimidazole

A mixture of (8.0 g, 51 mmol, 1.0 eq) 1-chloro-2-nitrobenzene and (5.54 g, 51 mmol, 1.0 eq) 4-aminophenol in 40 ml of dry dimethylsulfoxide was heated to reflux for 18 hours. The reaction mixture was cooled, poured into 400 ml of 0.1N HCl and 400 ml ethyl acetate, stirred, and filtered through celite. The filtrate layers were separated, and the aqueous layer was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H₂O, once with brine, dried over MgSO₄, and concentrated to give 8 g of a dark oil. Silica gel chromatography eluting with 20% ethyl acetate/hexane gave 1.63 g, 14%, of a red solid.

A mixture of (1.6 g, 6.89 mmol, 1.0 eq) 4-N-(2-nitrophenyl)amino phenol and 800 mg of 10% Pd/C in 100 ml ethyl acetate was placed on a Parr hydrogenation apparatus and shaken under 50 psi H₂ for 3 hours. The mixture was filtered through celite, concentrated in vacuo, and chromatographed on a silica gel column eluting with 50% ethyl acetate/hexane to give 1.3 g, 94%, of an orange-yellow solid.

A mixture of (600 mg, 3.00 mmol, 1.0 eq) 4-N-(2-aminophenyl)amino phenol and 10 ml valeric anhydride was heated to reflux for 18 hours. The mixture was taken up in 50 ml of methanol, basified with 2N NaOH to pH 10, and stirred 1 hour at room temperature. The reaction mixture was then neutralized and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H₂O, once with brine, dried over MgSO₄ and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 2½% CH₃OH-CH₂Cl₂ gave 124 mg, 16%, solid. M.P.: 192-194°C.

PREPARATION 39

4'-Methoxy-3'-(1-methyl-4-phenylbutoxy)- [1,1'-biphenyl]-4-carbonitrile

To a solution of (1.4 g, 4.01 mmol, 1.0 eq) of (±)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene in 40 ml dry THF at -78°C was added dropwise 1.76 ml (4.4 mmol, 1.1 eq) of 2.5M n-BuLi. After stirring 40 minutes at -78°C, (4.81 ml, 4.81 mmol, 1.2 eq) 1.0M ZnCl₂ in ether was added, and the mixture warmed to room temperature over 30 minutes. Pd(PPh₃)₄ (231 mg, 0.2 mmol, 0.05 eq) and (918 mg, 4.01 mmol, 1.0 eq) 4-iodobenzonitrile were added, and the mixture stirred 2 hours at room temperature. The

-133-

reaction mixture was concentrated in vacuo and chromatographed on silica gel eluting with ether-hexane (5-30%) to afford 1.1 g, 74%, of 4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-[1,1'-biphenyl]-4-carbonitrile. NMR (250 MHz, CDCl₃): 7.70 (2H, m); 7.59 (2H, m); 7.17 (7H, m); 6.96 (1H, m); 4.42 (1H, m); 3.90 (3H, s); 1.35 (3H, d, J=6.1 Hz).

PREPARATION 40

Methyl 1-(3-hydroxy-4-methoxyphenyl)- 1H-benzimidazole-5-carboxylate

A mixture of (10 g, 74.5 mmoles) 5-amino-2-methoxyphenol and (13.3 g, 62 mmoles) methyl 3-nitro-4-chlorobenzoate in 50 ml of pyridine was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate and washed with dilute HCl, then dried over MgSO₄ and evaporated to give 12.7 g of crude product which was triturated with CH₂Cl₂ and filtered to give 3.9 g of purified methyl 4-N(4-methoxy-3-hydroxyphenyl)amino-3-nitrobenzoate.

A solution of 3.9 g of the above nitro compound in 75 ml of methanol and 50 ml of THF and 400 mg of 10% palladium on charcoal was shaken on a Parr shaker, at 40 psi H₂ for 5 hours. The catalyst was removed by filtration and the solvent evaporated in vacuo. The product methyl 4-N(4-methoxy-3-hydroxyphenyl)amino-3-aminobenzoate (3.4 g) was used without purification.

A mixture of 3.4 g of the above amine and 900 mg of ethyl formate in 25 ml of formic acid was heated at 100° overnight. The solvents were evaporated in vacuo to give 1.6 g of the title product.

PREPARATION 41

2-N[3-(Cyclopentyloxy)-4-methoxyphenyl- carbonyl]amino-3-hydroxypyridine

A mixture of (1.2 g, 5 mmoles) of 4-methoxy-3-cyclopentyloxybenzoic acid and 25 ml of thionyl chloride was heated at reflux for 30 minutes. Excess thionyl chloride was removed in vacuo and the resulting acid chloride was used without purification.

The crude acid chloride from above was dissolved in THF and was added to a solution of 600 mg of 2-amino-3-hydroxypyridine in 5 ml of pyridine at 0°C. After stirring at 0°C for 2 hours, the reaction was allowed to stir at room temperature overnight. The volatiles were evaporated and the residue was triturated with H₂O and filtered to give 1.4 g of the desired amide. M.P. 165-166°C.

-134-

PREPARATION 42

3-Cyclopentyloxy-4-methoxybenzthioamide

4-Methoxy-3-cyclopentyloxybenzoic acid was converted to its acid chloride analogous to the procedure of Preparation 41.

The acid chloride (500 mg) was dissolved in 10 ml of THF and added dropwise to a solution of aqueous ammonium hydroxide at 0°C. After 30 minutes the reaction was extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 420 mg of product. M.P.: 167-168°C.

A mixture of 400 mg of the amide and 413 mg of Lawesson's reagent in 20 ml of toluene was heated at reflux for 1 hour. The volatiles were evaporated and the residue purified on silica gel with CH₂Cl₂/methanol to give 220 mg of product. M.P.: 145-147°C.

PREPARATION 43

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-methylthiazole

4-Methoxy-3-norbornyloxybenzoic acid was converted to the corresponding acid chloride using the procedure of Preparation 41.

To a solution of 6.9 gm of the acid chloride in 50 ml of ether was added dropwise to a solution of 2 equivalents of diazomethane in ether. The resulting diazoketone was then converted to chloromethyl ketone by addition of excess HCl(g). Evaporation of the volatiles gave 3.5 g of chloromethyl ketone which was used without purification.

A solution of 294 mg of chloromethyl ketone and 120 mg of thioacetamide in 5 mls of DMF was heated on a steam bath for 8 hours. The reaction was then poured onto H₂O and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 260 mg crude product. Purification on silica gel with CH₂Cl₂/ethyl acetate gave 90 mg of the title product, M.P. 81-82°C.

PREPARATION 441-(3-Hydroxy-4-methoxyphenyl)-
1H-imidazo[4,5-c]pyridine

A mixture of 5.7 g of 3-nitro-4-chloropyridine, 3 g of NaHCO₃ and 5 g of 5-amino-2-methoxyphenol in 100 ml of ethanol was stirred at room temperature overnight. The ethanol was evaporated and the residue slurried with hot THF to dissolve

-135-

the product. Evaporation of the THF gave 8.7 g of the nitro product used without purification.

The nitro compound from above (8.7 g) was reduced with H_2 and Pd/C on a Parr shaker during 5 hours. The reaction was filtered over celite and evaporated to give 8.2 g of the amine product.

A solution of 2.7 g of the amino pyridine from above in 75 ml of formic acid containing 1.7 g of ethyl formate was heated at 100°C for 8 hours. The volatiles were evaporated and the residue was treated with methanolic NaOH at 100°C for 2 hours. The reaction was cooled and the pH adjusted to 7.0 with 1N HCl. The resulting solid was filtered and dried to give 2.05 g of product. M.P.: 231-233°C.

PREPARATION 45

1-(5-Bromo-2-methoxyphenoxy)- 5-(4-fluorophenyl)pentane

(a) Preparation of 6-(4-fluorophenyl)-1-hexene

A suspension of 6-bromo-1-hexene (10 g), magnesium (1.5g), and iodoethane (1 drop) in anhydrous tetrahydrofuran was heated at reflux until all of the magnesium dissolved. The resulting Grignard reagent was cooled to about 0°C and was treated with a 1M solution of $ZnCl_2$ in ether (67 ml), and the mixture was allowed to warm to room temperature over 30 minutes. Tetrakis(triphenylphosphine)palladium (0) (3.5 g) and 4-bromofluorobenzene (6.73 ml) were added to the reaction and the mixture was heated to reflux for 1 hour. The mixture was cooled to room temperature, concentrated in vacuo, diluted with hexane, filtered and concentrated once more in vacuo. Chromatography on a silica gel column eluting with ether-hexane (0-5%) afforded 5 g of a colorless oil.

(b) Preparation of 5-(4-fluorophenyl)pentanal

The above oil (2.5 g) was dissolved in 1:9 methanol-methylenechloride (50 ml), cooled to about -78°C and treated with ozone gas until the mixture became light blue. At this time ozone addition was ceased and the mixture was purged with nitrogen gas. Triphenylphosphine (5 g) was added and the mixture was allowed to stand at room temperature over 24 hours. The reaction mixture was concentrated in vacuo, diluted with ether, filtered and concentrated once more in vacuo. Chromatography on a silica gel column eluting with ethyl acetate-hexane (10-20%) gave 1.3 g of aldehyde as a colorless oil.

-136-

(c) Preparation of 5-(4-fluorophenyl)pentanol

The above aldehyde (1.3 g) was dissolved in methanol (20 ml) at about 0°C and treated with sodium borohydride (1.0 g). After 10 minutes the mixture was quenched with saturated aqueous ammonium chloride, and was extracted with ether. The combined organics were washed with water followed by brine, dried over sodium sulfate, filtered and concentrated in vacuo. Filtration through silica gel gave 1.2 g as a colorless oil.

(d) Preparation of the title compound

1-(5-Bromo-2-methoxyphenoxy)-5-(4-fluorophenyl)pentane was prepared from 5-bromoguaiacol and 5-(4-fluorophenyl)pentanol as in Preparation 11. M.P.: 46-47°C.

PREPARATION 46

1-(5-Bromo-2-methoxyphenoxy)-
4-(4-fluorophenoxy)butane

(a) Preparation of 4-(4-fluorophenoxy)-1-butene

A solution of 4-bromo-1-butene (4.0 g), 4-fluorophenol (3.0 g), potassium carbonate (3.8 g) and acetone (75 ml) was heated at reflux over 16 hours. The mixture was then concentrated in vacuo, diluted with ether, washed with water followed by 1N sodium hydroxide, dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on a silica gel column eluting with 25% ethyl acetate-hexane afforded 1.6 g of a colorless oil.

(b) Preparation of 1-bromo-4-(4-fluorophenoxy)butane

Anhydrous HBr was bubbled through a mixture of the above oil (1.6 g) and benzoyl peroxide (0.136 g) in petroleum ether (60 ml) kept below 15°C using an ice-bath. After 30 minutes the system was purged with nitrogen, diluted with petroleum ether (50 ml) and washed with saturated aqueous sodium bicarbonate and brine. The mixture was then dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography on a silica gel column eluting with ethyl acetate-hexane (5-10%) afforded 2.08 g as a colorless oil.

(c) Preparation of the title compound

A mixture of the above oil (2.08 g), 5-bromoguaiacol (1.71 g), potassium carbonate (3.5 g) and dimethylformamide (35 ml) was stirred at about 80°C over 3 hours. The mixture was cooled to room temperature, poured into water (250 ml) and extracted with 20% ethyl acetate-hexane. The combined organics were washed with brine, dried over sodium sulfate and concentrated in vacuo. Chromatography on a

-137-

silica gel column eluting with 25% ethyl acetate-hexane afforded 2.27 g of a white crystalline solid. M.P.: 44-47°C.

PREPARATION 47

4-Methoxy-3-(5-phenylpentoxy)benzoic acid

To a magnetically stirred solution of 4-methoxy-3-(5-phenylpentoxy)-benzaldehyde (9.90 grams, 33.2 mmols) and 2-methyl-2-butene (56.2 ml, 530 mmols) in *tert*-butanol (300 ml) was added a solution of sodium chlorite (24.0 grams) and sodium phosphate monobasic (24.0 grams) in water (200 ml) over 10 minutes. After stirring vigorously for about 30 minutes the mixture was concentrated under reduced pressure and acidified to pH 2 with 6N HCl. The precipitate was filtered and dried to give 9.4 grams of a white solid, MS m/z [M]⁺ 314.

PREPARATION 48

4-[(5-Bromo-2-methoxy)phenoxy]butanoic acid ethyl ester

A mixture of 15.0 g (0.0740 mol) of 2-methoxy-4-bromophenol, 17.4 g (0.0890 mol) of ethyl 4-bromobutyrate, 20.5 g (0.148 mol) of K₂CO₃, and 200 ml of DMF was stirred at about 80°C and continued for about 16 h. The combined ether extracts were washed with brine (1 x 300 ml), dried (MgSO₄), and evaporated to give 26.0 g of an orange oil. Purification by flash chromatography using an ethyl acetate-hexane (1:4) eluant gave 19.7 g (84%) of the title compound as a clear oil (R_f 0.5 EtOAc-hexane, 3:7). ¹H-NMR (CDCl₃) δ 1.25 (3H, t, J=7), 2.09-2.18 (2H, m), 2.51 (2H, t, J=7), 3.82 (3H, s), 4.03 (2H, t, J=7), 4.13 (2H, q, J=7), 6.72 (1H, d, J=8), 6.97-7.08 (2H, m).

PREPARATION 49

4-[(5-Bromo-2-methoxy)phenoxy]butanal

A solution of 1.50 g (4.72 mmol) of the compound of Preparation 48 in 15 ml of dry THF was chilled to about -78°C and was treated dropwise with 7.08 ml (7.08 mmol) of a solution of 1.0 M diisobutylaluminum hydride in hexane at such a rate that the reaction temperature did not rise above -60°C. After stirring an additional 0.5 h, 5 ml of methanol was added dropwise. After the exotherm had subsided, 25 ml of 1N HCl was added and the mixture was allowed to warm to room temperature. The THF and methanol was removed by evaporation, and the residue was diluted with 150 ml of 1N HCl and was extracted with EtOAc (2 x 100 ml). The combined extracts were washed with saturated NaHCO₃ solution (2 x 100 ml), brine (1 x 100 ml), dried (MgSO₄), and evaporated to give 1.25 g of a clear oil. Purification by flash chromatography using an EtOAc-hexane eluant (3:7) afforded 523 mg (41%) of the title compound as a clear oil.

-138-

(R_f 0.5 EtOAc-hexane, 1:1). $^1\text{H-NMR}$ δ 2.10-2.20 (2H, m), 2.68 (2H, t, $J=6$), 3.80 (3H, s), 4.00 (2H, t, $J=6$), 6.71 (1H, d, $J=9$), 6.95-7.04 (2H, m), 9.82 (1H, s).

PREPARATION 50

4-(5-Bromo-2-methoxy)phenoxy-1-(3,4-dimethyl)phenyl-1-butanol

A solution of 176 mg (0.952 mmol) of 4-bromo-*o*-xylene in 5 ml of dry THF was chilled to about -78°C and was treated dropwise with 0.322 ml (0.805 mmol) of a 2.5 M solution of *n*-Buli in hexane. When the exotherm had subsided, the mixture was stirred an additional 10 min, and a solution of 200 mg (0.732 mmol) of the compound of Preparation 49 in 5 ml of THF was added. The mixture was stirred an additional 20 min and was quenched by the addition of saturated aqueous NH_4Cl solution. After warming to room temperature, the THF was removed by evaporation and the residue was diluted to 100 ml with water and was extracted with EtOAc (2 x 100 ml). The extracts were combined, dried (Na_2SO_4), and evaporated to give 400 mg of a clear oil. Purification by flash chromatography using an EtOAc-hexane eluant (3:7) afforded 172 mg (62%) of the title compound as an oil (R_f 0.4 EtOAc-hexane). $^1\text{H NMR}$ (CDCl_3): δ 1.81-1.87 (4H, m), 2.22 (3H, s), 2.23 (3H, s), 3.89 (3H, s), 3.96-4.01 (2H, m), 4.60-4.69 (1H, m), 6.66 (1H, d, $J=9$), 6.87-7.08 (5H, m).

PREPARATION 51

4-Carbomethoxy-2-methylphenylboronic acid

To a solution of 50.0 g (0.232 mol) of 4-bromo-3-methylbenzoic acid in 500 ml of dry THF at about -78°C was added dropwise 300 ml (0.511 mol) of a 2.5 M solution of *n*-Buli in hexane over a period of about 0.5 h. After 20 min. of additional stirring at about -78°C , 64.0 g (0.278 mol) of tributylborane was added dropwise. The mixture was stirred an additional 3 h at about -78°C , and, following removal of the ice bath, 500 ml of 1N HCl solution was added carefully. The mixture was stirred for about 16 h at room temperature and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 50 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was triturated in hexane and 16 g of a white solid was removed by filtration. The mother liquor was concentrated and was purified by flash chromatography using an EtOAc-hexane eluant (3:7 to 1:1) to give 4.00 g of crude 4-carboxy-2-methylphenylboronic acid; (R_f 0.1 EtOAc-hexane, 1:1). This material was dissolved in 60 ml of thionyl chloride and was refluxed for 1 h. The excess thionyl chloride was removed by distillation under reduced pressure, and the oily residue was diluted with 100 ml of methanol. The mixture was stirred for about 16 h at room

-139-

temperature and the methanol was removed by evaporation. The residue was purified by flash chromatography using an EtOAc-hexane eluant (3:7 to 1:1) to afford 2.35 g (4%) of the title compound as a white solid (R_f 0.35 EtOAc-hexane, 1:1). $^1\text{H-NMR}$ (DMSO- d_6): δ 2.68 (3H, s), 3.81 (3H, s), 7.66-7.72 (2H, m), 7.93 (1H, d, $J=8$).

PREPARATION 52

4-[3-[4-(3,4-Dimethylphenyl)-4-hydroxy]butyloxy-4-methoxy]phenyl- 3-methylbenzoic acid methyl ester

To a solution of 170 mg (0.448 mmol) of the compound of Preparation 49 in 4 ml of toluene was added 17 mg of tetrakis(triphenyl)phosphinepalladium, a solution of 82 mg (0.448 mmol) of the compound of Preparation 51 in 2 ml of EtOH, and 0.670 ml of saturated aqueous solution of Na_2CO_3 . The resulting mixture was heated to reflux for about 4 h. The mixture was partially evaporated to remove toluene and ethanol, and the residue was diluted with EtOAc and was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give 228 mg of a brown oil. Purification by flash chromatography with an EtOAc-hexane eluant (3:7) afforded 72 mg (36%) of the title compound as a foam (R_f 0.45 EtOAc-hexane 1:1). $^1\text{H-NMR}$: δ 1.82-1.97 (4H, m), 2.20 (3H, s), 2.21 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.97-4.08 (2H, m), 4.63-4.72 (1H, m), 6.73-7.25 (6H, m), 7.82 (1H, d, $J=8$), 7.88 (1H, s).

PREPARATION 53

4-Bromo-4-methoxy-3-[(4-aminophenyl)butyloxy]benzene

A mixture of 298 mg (1.09 mmol) of the compound of Preparation 49, 11 mg (1.20 mmol) of aniline, and 5 ml of MeOH was stirred at room temperature for about 1 h. The mixture was chilled to about 0°C and was treated with 46 mg (1.22 mmol) of NaBH_4 . After stirring for about 2 h at about 0°C , excess 1N HCl was added and the mixture was partially evaporated to remove MeOH. The residue was overlaid with EtOAc, and the aqueous layer was basified to pH 8. The organic layer was separated and was combined with two EtOAc extracts of the aqueous layer. The combined organic extracts were dried (Na_2SO_4) and evaporated to give an oil, which was purified by flash chromatography using an EtOAc-hexane eluant (1:4) to afford 135 mg (35%) of the title compound as an oil (R_f 0.4 EtOAc-hexane, 3:7). $^1\text{H-NMR}$ δ : 1.77-1.94 (4H, m), 3.19 (2H, t, $J=6$), 3.81 (3H, s), 4.00 (2H, t, $J=6$), 6.58-7.16 (8H, m).

-140-

PREPARATION 54

4-[3-[(4-Aminophenyl)butyloxy]-4-methoxy]phenyl-
3-methylbenzoic acid methyl ester

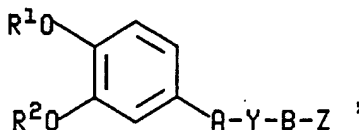
Following the same procedures in Preparation 52, 1.88 mg (0.536 mmol) of the compound of Preparation 53 and 109 mg (0.590 mmol) of the compound of Preparation 51 were coupled to give 193 mg (86%) of the title compound. Purification was performed by flash chromatography using an EtOAc-hexane (1:4) eluant. ¹H-NMR δ 1.80-2.02 (4H, m), 2.32 (3H, s), 3.21 (2H, t, J=7), 3.91 (s, 3H), 3.93 (s, 3H), 4.06 (2H, t, J=6), 6.60-7.30 (9H, m), 7.87 (1H, d, J=8), 7.93 (1H, s).

-141-

CLAIMS

What is claimed is:

1. A compound of the formula



(I)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically acceptable salts thereof wherein

R¹ is selected from the group consisting of methyl, ethyl, difluoromethyl and trifluoromethyl;

R² is selected from the group consisting of (C₁-C₆)alkyl, alkoxyalkyl having 3 to 7 carbons in the alkoxy portion and 2 to 4 carbons in the alkyl portion, phenoxyalkyl having 2 to 6 carbons in the alkyl portion, (C₃-C₇)cycloalkyl, (C₆-C₉)polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion, phenylaminoalkyl having 2 to 6 carbons in the alkyl portion and the amino may be optionally substituted with (C₁-C₄)alkyl and indanyl,

where the alkyl portion of said alkyl, phenoxyalkyl, cycloalkyl, polycycloalkyl, phenylalkyl and indanyl may optionally be substituted with one or more fluorine atoms, -OH or (C₁-C₄)alkoxy,

and the aryl portion of said phenylalkyl, phenoxyalkyl and indanyl may optionally be substituted with (C₁-C₄)alkyl, (C₁-C₄)alkoxy or halogen;

A and B are independently selected from the group consisting of a covalent bond, optionally substituted (C₁-C₅)alkylene, optionally substituted (C₂-C₅)alkenyl and optionally substituted phenylene,

where said optionally substituted alkylene may be monosubstituted and each substituent is selected from the group consisting of oxo, (C₁-C₄)alkoxy, CO₂R⁶ and hydroxy,

said optionally substituted alkenyl may be monosubstituted with (C₁-C₄)alkoxy or CO₂R⁶, and

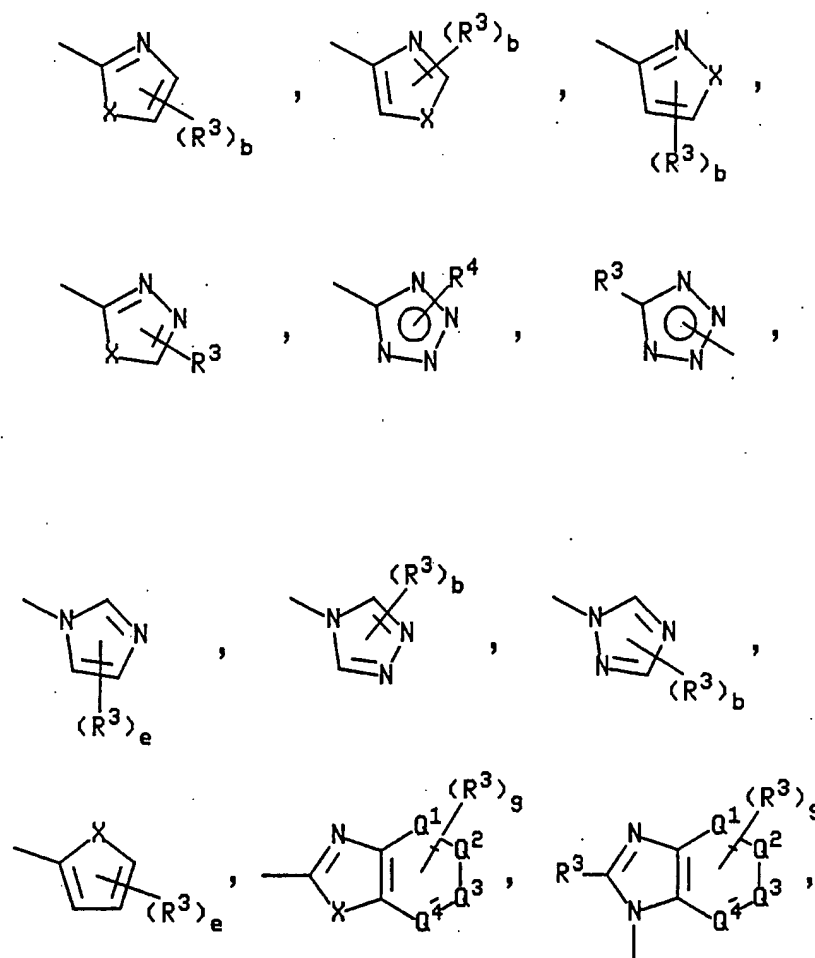
said optionally substituted phenylene may be monosubstituted with (C₁-C₄)alkoxy, CO₂R⁶ or hydroxy,

wherein R⁶ is hydrogen or (C₁-C₄)alkyl;

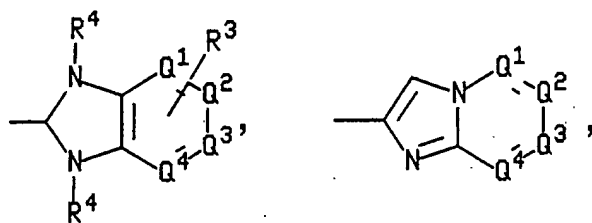
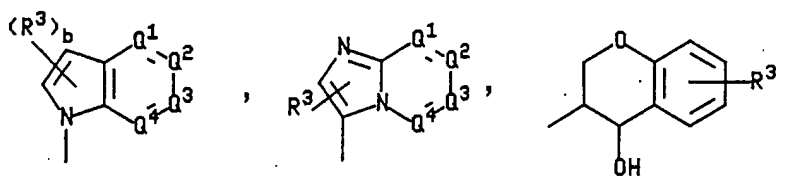
-142-

Y is selected from the group consisting of a covalent bond, O, NR^6 and S wherein R^6 is as defined above;

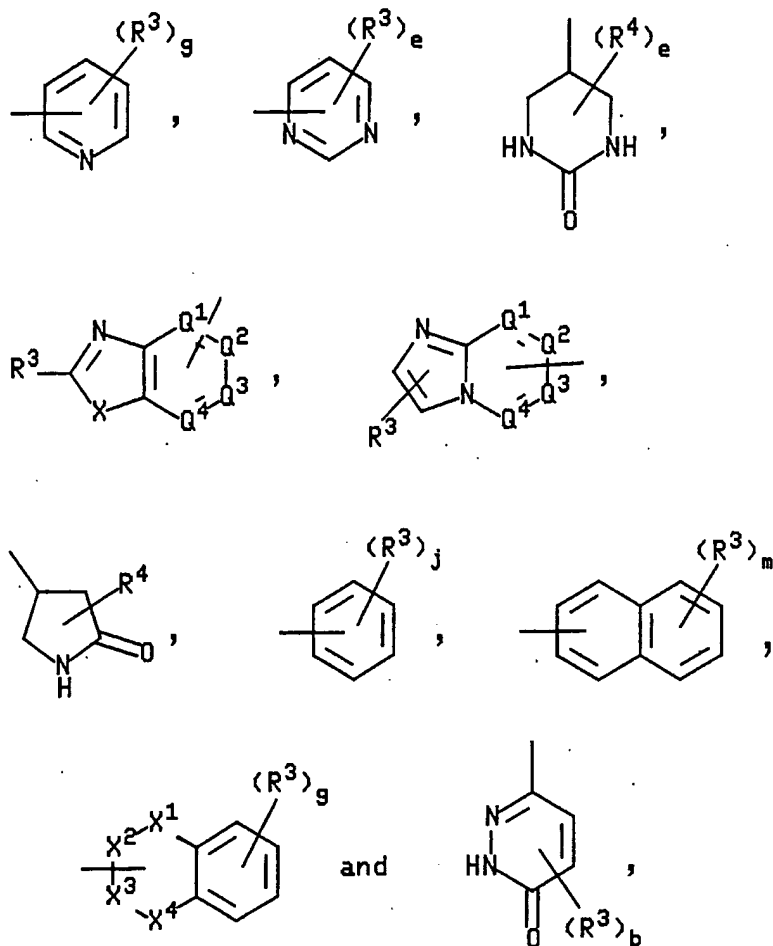
Z is selected from the group consisting of



-143-



-144-



where Q^1 , Q^2 , Q^3 , and Q^4 are independently N, CH or, when also bonded to B, C and provided that at least two of Q^1 , Q^2 , Q^3 , and Q^4 are not N;

X is selected from the group consisting of O, NR^4 and S;

and X^1 , X^2 , X^3 and X^4 are independently selected from the group consisting of O, NR^4 , S, C=O, CH_2 and, when also bonded to B, CH;

b is an integer from 1 to 2;

e is an integer from 1 to 3;

g is an integer from 1 to 4;

j is an integer from 1 to 5;

m is an integer from 1 to 7;

-145-

each R^3 is independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, $CH(R^7)CO_2R^4$, (C_1-C_6) alkoxy, CO_2R^4 , $CONR^4R^5$, $CONHOH$, $CH_2NR^4R^5$, NR^4R^5 , nitro, hydroxy, CN, SO_3H , phenylalkyl having 1 to 4 carbons in the alkyl portion, $SO_2NR^4R^5$, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, phenyl optionally substituted with (C_1-C_4) alkyl or halogen, $CH(R^7)CO_2R^6$, (C_3-C_7) cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion and dialkylaminoalkyl having a total of 5 carbons in the dialkylamino portion and having 2 to 5 carbons in the alkyl portion where R^6 is as defined above,

R^5 for each occurrence is independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion, phenyl, pyridyl, pyrimidyl, thiazolyl and oxazolyl,

or R^4 and R^5 are taken together with the nitrogen to which they are attached and form an optionally substituted saturated or unsaturated 5- or 6-membered ring, a saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms, or a quinoline ring optionally substituted with fluoro,

where said optionally substituted saturated or unsaturated 5- or 6-membered ring may be mono- or di-substituted and each substituent is independently selected from the group consisting of alkyl having 1 to 4 carbons, CO_2R^7 wherein R^7 is as defined below, $CONH_2$, $CON(CH_3)_2$, oxo, hydroxy, NH_2 and $N(CH_3)_2$, and said saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms has the second heteroatom selected from the group consisting of O, S, NH, NCH_3 , $NCOCH_3$ and NCH_2Ph ;

R^7 for each occurrence is independently selected from the group consisting of hydrogen and (C_1-C_4) alkyl;

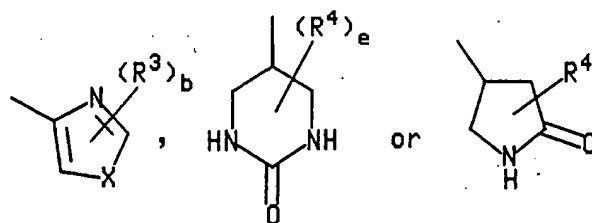
and R^8 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl and phenylalkyl having 1 to 4 carbons in the alkyl portion;

with the proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9) polycycloalkyl or indanyl; A, B and Y are covalent bonds; X is N; and R^3 is hydrogen;

then Z is not

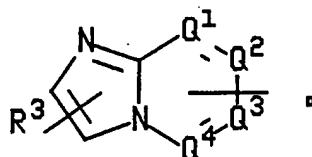
-146-



and with the further proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9) polycycloalkyl or indanyl; A, B and Y are covalent bonds; Q^1 , Q^2 , Q^3 , and Q^4 are CH or, when bonded to B, C; and R^3 is hydrogen;

then Z is not



2. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

R^1 is selected from the group consisting of methyl and difluoromethyl;

R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion;

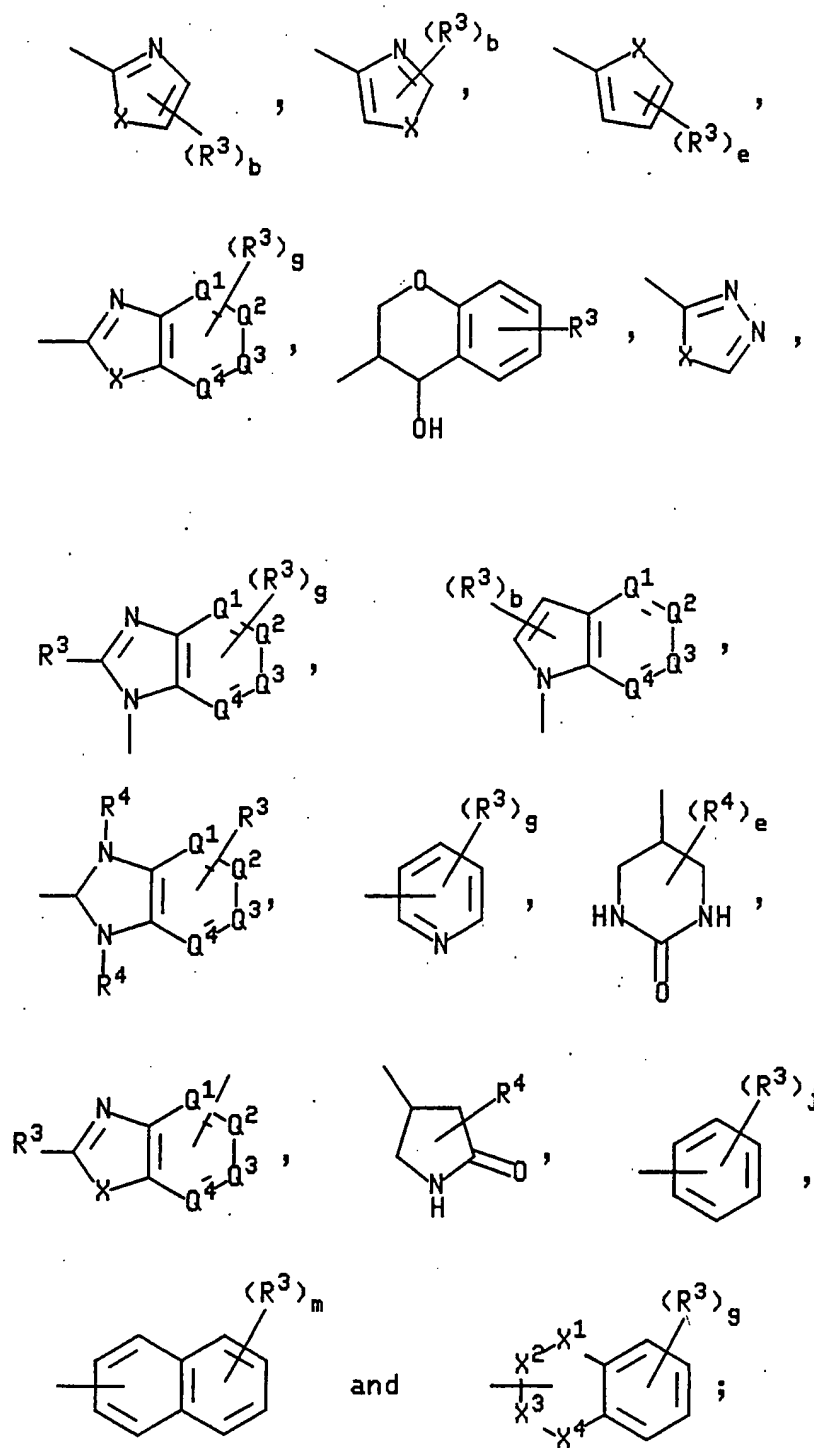
A is selected from the group consisting of a covalent bond, (C_1-C_5) alkylene and (C_2-C_5) alkenyl;

B is selected from the group consisting of a covalent bond, phenylene optionally substituted with (C_1-C_4) alkoxy, (C_1-C_5) alkylene and (C_2-C_5) alkenyl;

Y is selected from the group consisting of a covalent bond, O and NR^6 ;

Z is selected from the group consisting of

-147-



-148-

each R^3 is independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, $CH(R^7)CO_2R^4$, (C_1-C_6) alkoxy, CO_2R^4 , $CONR^4R^5$, nitro, hydroxy, $N(SO_2R^6)_2$ and $NHSO_2R^6$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen and (C_1-C_6) alkyl and

R^5 is selected from the group consisting of hydrogen and (C_1-C_6) alkyl.

3. A compound or a pharmaceutically acceptable salt thereof according to claim 2, wherein

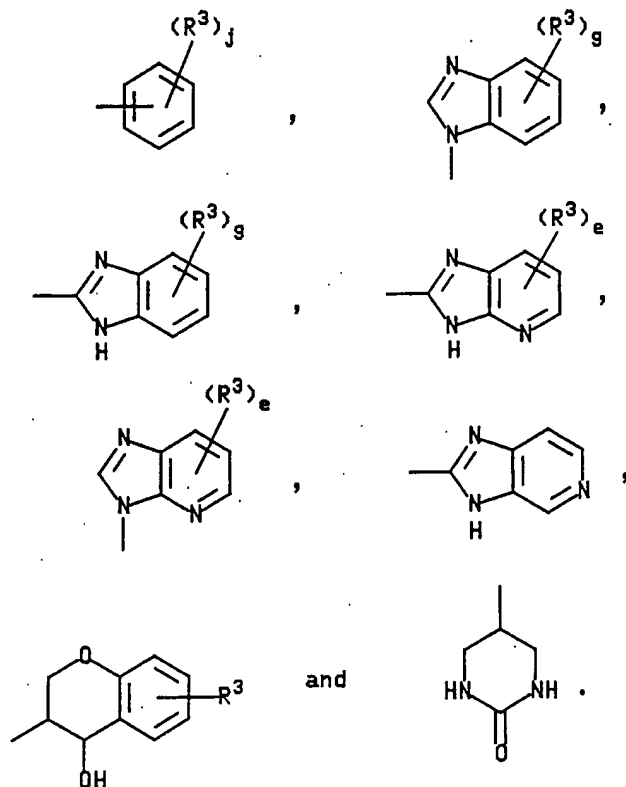
R^2 is selected from the group consisting of (C_3-C_7) cycloalkyl, (C_6-C_9) polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion;

A is selected from the group consisting of a covalent bond and methylene;

B is selected from the group consisting of a covalent bond, methylene and phenylene;

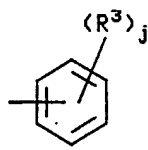
Y is selected from the group consisting of a covalent bond and O; and

Z is selected from the group consisting of

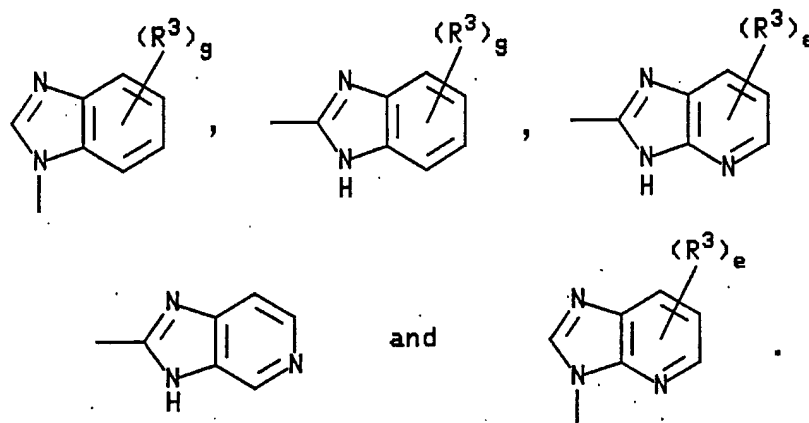


-149-

4. A compound or a pharmaceutically acceptable salt thereof according to

claim 3, wherein A, B and Y are a covalent bond; and Z is 

5. A compound or a pharmaceutically acceptable salt thereof according to claim 3, wherein A, B and Y are a covalent bond; and Z is selected from the group consisting of

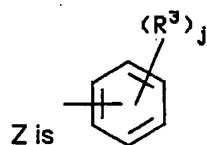


6. A compound or a pharmaceutically acceptable salt thereof according to claim 3 wherein

A is methylene;

B is a covalent bond;

Y is O; and

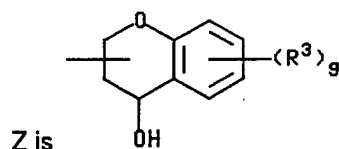


7. A compound or a pharmaceutically acceptable salt thereof according to claim 3 wherein

A is methylene;

B and Y are a covalent bond; and

-150-



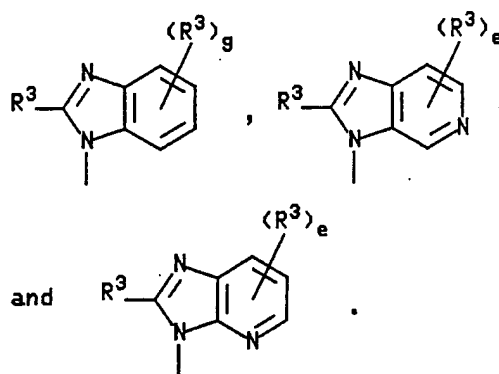
8. A compound or a pharmaceutically acceptable salt thereof according to claim 2 wherein

A is methylene;

B is phenylene;

Y is O; and

Z is selected from the group consisting of



9. A pharmaceutical composition comprising an amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1 and a pharmaceutically acceptable diluent or carrier.

10. A method of inhibiting phosphodiesterase IV in a mammal in need thereof which comprises administering to said mammal a phosphodiesterase IV inhibiting amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

11. A method of treating an inflammatory condition in a mammal which comprises administering to said mammal an antiinflammatory amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

12. A method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis or shock in a mammal which

-151-

comprises administering to said mammal an effective amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 93/10228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C65/21 A61K31/085 A61K31/19 A61K31/235 C07C69/76
 C07C205/35 C07C205/57 C07C311/02 C07C311/51 C07C235/42
 C07C235/34 C07C217/58 C07C217/80 C07C219/14 C07C255/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 19594 (SMITH KLINE BEECHAM) 12 November 1992 see page 6, line 6 - line 23; claim 1 ---	1,9
X	EP,A,0 511 865 (AMERICAN HOME PRODUCTS) 4 November 1992 see page 3, line 1 - line 41; claim 1 ---	1,9
X	WO,A,92 06963 (BYK GULDEN LOMBERG) 30 April 1992 see claims 1,8 ---	1,9
X	WO,A,84 04521 (BYK GULDEN LOMBERG) 22 November 1984 see page 3, line 29 - line 35; claim 1 ---	1,9
X	WO,A,87 06576 (PFIZER) 5 November 1987 see page 25, line 1 - line 20; claim 1 ---	1,9
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

18 March 1994

Date of mailing of the international search report

30.03.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 93/10228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C271/02 C07C259/10 C07D213/79 C07D239/10 C07D401/14
 C07D401/06 C07D207/26 C07D311/22 C07D279/16 C07D237/14
 C07D471/04 C07D235/06 C07D333/38 C07D257/04 C07D209/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 428 313 (PFIZER) 22 May 1991 see claims 1,7 ---	1,9
X	EP,A,0 428 302 (PFIZER) 22 May 1991 see claims 1,13 ---	1,9
X	CHEMICAL ABSTRACTS, vol. 115, no. 15, 1991, Columbus, Ohio, US; abstract no. 158680z, G. WANG ET AL. 'A convenient method for the conversion of alpha-tetralones to aryl acetates' page 891 ; see abstract and 12th collective index, page 57274, column 3, lines 87-91 & SYNTH. COMMUN. 1991, 21(8-9), 989-96 --- -/--	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
 'E' earlier document but published on or after the international filing date
 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 'O' document referring to an oral disclosure, use, exhibition or other means
 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 '&' document member of the same patent family

Date of the actual completion of the international search

18 March 1994

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/10228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D277/32 C07D277/22 C07D277/64 C07D513/04 C07D498/04
 C07D285/12 C07D233/60 C07D231/12 C07D235/18 C07D233/90
 A61K31/16 A61K31/325 A61K31/275 A61K31/135 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 19, 1990, Columbus, Ohio, US; abstract no. 172319h, M. AKASU ET AL. 'Anticancer agents containing 1-benzylisoquinolines' page 80 ; see abstract & JP,A,01 233 221 (KAKEN) 19 September 1989	1,9
X	WO,A,92 06085 (SMITH KLINE & FRENCH) 16 April 1992 see claim 10 and examples 12,24,29,35,43	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
 'E' earlier document but published on or after the international filing date
 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 'O' document referring to an oral disclosure, use, exhibition or other means
 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

18 March 1994

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 93/10228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 A61K31/38 A61K31/395 //(C07D471/04, 235:00, 221:00),
(C07D513/04, 277:00, 221:00), (C07D498/04, 263:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

18 March 1994

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/ 10228

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10-12 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
On grounds of Articles 6 and 17.2a(11) of the PCT (conciseness of claims) and of the Guidelines for Examination in the EPO, Part B, Chapter III, 2.2 (economic reasons) the search has been based on the preparation examples disclosed in the description.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JS 93/10228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9219594	12-11-92	AU-A- 1917092 CN-A- 1067244 EP-A- 0584208	21-12-92 23-12-92 02-03-94
EP-A-0511865	04-11-92	US-A- 5191084 AU-A- 1524492 JP-A- 5117239 US-A- 5250700	02-03-93 05-11-92 14-05-93 05-10-93
WO-A-9206963	30-04-92	AU-A- 8722991 CA-A- 2094127 EP-A- 0553174	20-05-92 17-04-92 04-08-93
WO-A-8404521	22-11-84	AU-B- 560607 AU-A- 2961784 CA-A- 1247100 DE-A- 3417391 EP-A,B 0125636 JP-T- 60501258 US-A- 4707481	09-04-87 04-12-84 20-12-88 15-11-84 21-11-84 08-08-85 17-11-87
WO-A-8706576	05-11-87	EP-A- 0247725 SU-A- 1646488 SU-A- 1653542	02-12-87 30-04-91 30-05-91
EP-A-0428313	22-05-91	WO-A- 9107177 AU-B- 627631 AU-A- 6653690 CA-A- 2029704 WO-A- 9107178	30-05-91 27-08-92 01-08-91 14-05-91 30-05-91
EP-A-0428302	22-05-91	WO-A- 9107501 CA-A- 2029705	30-05-91 14-05-91
JP-A-01233221	19-09-89	NONE	
WO-A-9206085	16-04-92	AU-B- 644016 AU-A- 8543191 CA-A- 2091989 EP-A- 0550576	02-12-93 28-04-92 29-03-92 14-07-93

information on patent family members

PC7, JS 93/10228

Form PCT/ISA/210 (patent family annex) (July 1992)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.